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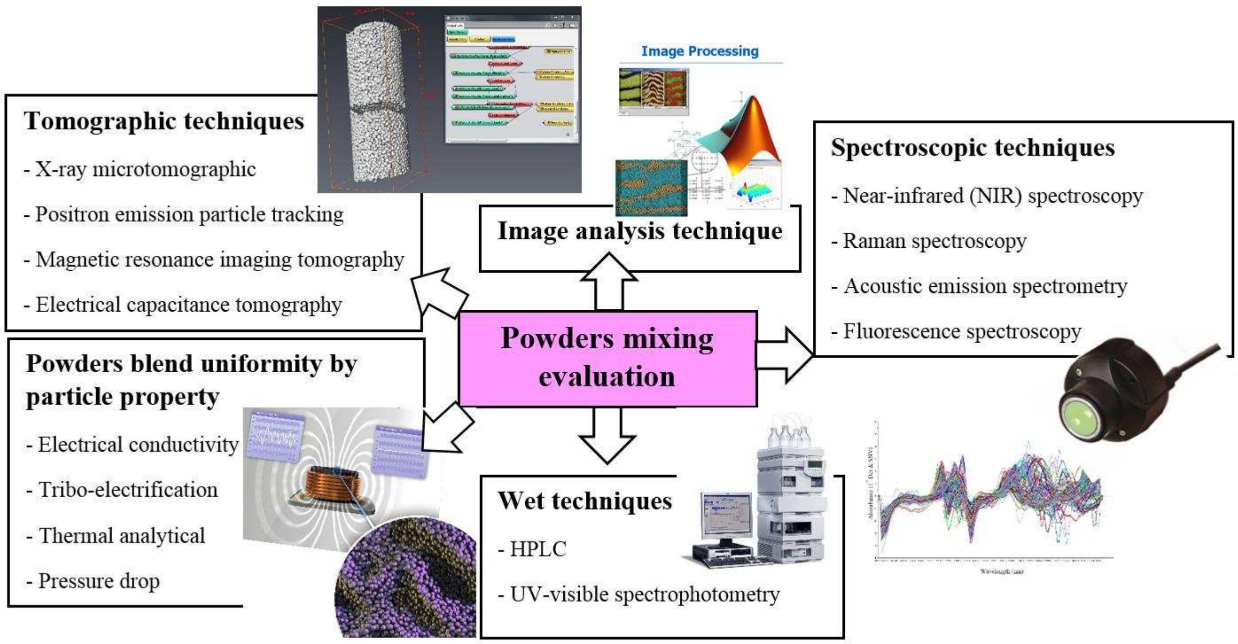
*Graphical Abstract (for review)



A review of current techniques for the evaluation of powder mixing

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ABSTRACT

Blending a mixture of powders to a homogeneous system is a crucial step in many manufacturing processes. To achieve a high quality of the end product, powder mixtures should be made with high content uniformity. For instance, producing uniform tablets depends on the homogeneous dispersion of active pharmaceutical ingredient (API), often in low level quantities, into excipients. To control the uniformity of a powder mixture, the first required step is to estimate the powder content information during blending. There are several powder homogeneity evaluation techniques which differ in accuracy, fundamental basis, cost and operating conditions. In this article, emerging techniques for the analysis of powder content and powder blend uniformity, are explained and compared. The advantages and drawbacks of all the techniques are reviewed to help the readers to select the appropriate equipment for the powder mixing evaluation. In addition, the paper highlights the recent innovative on-line measurement techniques used for the non-invasive evaluation of the mixing performance.

Keywords: Powder mixing evaluation, Powder blend homogeneity, Wet techniques, Dry techniques

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1. Introduction

Powder mixing unit operation is a very common step in particulate processes and has significant impact on the quality of the end product; examples are in industries such as pharmaceutical, agro-food, cement and plastics [1-8]. The final characteristics of the powdered products nowadays are becoming more complex. In some cases, a mixture of up to 20 powder ingredients is necessary to meet acceptable quality standard of the final product. Powder segregation, a phenomenon which is described as the opposite of mixing, or reverse mixing, takes place as a result of powder in-homogeneity during blending process or during secondary processing steps such as packaging and transportation [9-11]. A batch of pharmaceutical tablets at a cost of thousands of dollars could be rejected due to powder in-homogeneities arising from segregation of active component. As another example, layer by layer deposition of the segregated powders before getting fused together by laser, could adversely affect the quality of products in 3D printing manufacturing.

Mixing processes of granular materials often aim at producing a product with a suitable degree of homogeneity. There are two main types of equipment available for the mixing of granular materials. In the first group, the container is rotated around an axis to move around the materials inside to mix them with a dominant shear and diffusion mixing mechanisms. On the other hand, convection and/or shear could be the main mechanism in the second group in which the container is stationary and an internal rotor causes a mild or fast agitation. For the mixing of granular materials, the choice of mixer type is vital as the quality of the mixture highly depends on the mixer selection [12]. In addition, the quality of the mixture and the end-point of the process should be interpreted by evaluating the samples taken from the mixture. The goal of powder sampling is to collect a small amount of sample from a bulk powder in such a way that the sample represents the physical and chemical characteristics of the entire bulk. It should be noted that acquiring a representative sample from the bulk powder is crucial because further analyses and data interpretation regarding the mixing process performance depends on the sampling representativity [13].

It should be noted that developing a general guidance for obtaining a representative sampling is challenging and beyond the scope of this article since the conditions of mixing processes are different from case to case. However, a brief description of sample representativity procedure has been provided here and the readers are referred to the additional sources on this topic [7, 14, 15].

To apply a proper sampling procedure on bulk powders, the population and sample size, sample collection and sample size reduction method, and statistical analysis confirming the stated level of acceptance of the sampling plan must be fully addressed [16, 17]. A general framework of the sampling used in powder mixing processes is illustrated in Fig. 1-a.

The scale of scrutiny according to the product specification is mainly used to determine the ideal size of samples. The taken samples having the required size of scale of scrutiny must be analysed for the composition evaluation [12]. Generally, sample size should be close to the size of the final product, e.g. tablet size in pharmaceutical industry. Moreover, the sample size should be larger than the minimum amount needed for the analytical analysis. It should be noted that if the scale of scrutiny is defined too small, the homogeneity of the blend would wrongly appear to be unacceptable. In contrast, if the sample size is considered too large, the homogeneity of the blend would wrongly appear to be acceptable resulting in an overestimation of the homogeneity (Fig. 1-b). If the scale of scrutiny is much smaller than the minimum amount of sample that the sampler provides, reliable sample reduction techniques, which have been fully reviewed by Allen [18], must be applied. The granules segregation during sample reduction process must be prevented to have representative sub-samples which meet the scale of scrutiny. Cone and quartering, scoop sampling, rotary riffler, chute riffler and table riffler are among the most well-known and applied methods for sample splitting. Allen reported the representivity of all the methods (based on standard deviation in size distribution observed between different subsamples generated from the same primary sample) and introduced the rotary riffler as the most representative method for sample size reduction [18].

Fig. 1. (a) A general framework of sampling in powder mixing processes, (b) effect of the scale of scrutiny on mixing evaluation.

Powder sampling in a dynamic mixing process (Fig. 1-a) must be performed based on Golden Rules as follows [19]:

-Rule 1: Powder mixtures should be sampled when in motion.

-Rule 2: The whole stream of the powder mixture should be taken for many short increments of time, rather than part of the stream being taken for the whole time.

Acquisition of samples at the outlet of a continuous mixer should be performed at a regular frequency (starting at 3 times the residence time of the mixer when the system has reached a steady state). Full stream samplers at the outlet of the mixer are used in continuous mixers [19]. In a batch mixer, the mixer needs to be stopped at different blending times and then the sampling is carried out at various locations (by dividing the space into equal regions). Regarding the location of sampling, the whole powder stream should be sampled for numerous short increments of time [19].

The traditional samplers, e.g. thief and cross-cut, are most commonly used instruments for powder sampling [20]. Using samplers is mostly an invasive approach which causes disturbance in the mixture, hence special care and designs are needed to mitigate it [15, 21, 22]. However, in recent decades, non-invasive analytical technologies have been developed such as Near-Infrared spectroscopy (NIR), Raman spectroscopy and Electrical Capacitance Tomography with no interference with the blending process [23].

To control the uniformity of a mixture and reduce its inhomogeneity during blending, it is necessary to monitor the component concentration inside the mixer. This helps to achieve the optimum mixing conditions, such as end-point mixing time. Process monitoring can be achieved by performing routine testing of the process samples using off-line, at-line, inline and on-line instrumentations. Off-line analyser is a discontinuous, invasive, slow and time consuming traditional laboratory method that is performed in a controlled location by a technically trained person. For this purpose, the samples removed from the process are transported to a laboratory for further analysis. Its advantage lies in the fact that it provides the greatest flexibility in selecting the measurement method, sample preparation and the most accurate method [24]. Procedure of at-line analyser is similar to that of off-line, however, the main difference is the time duration of the analysis. Usually, at-line analysis can be performed with automatic facilities quicker than off-line analysis by a mediocre operator. For at-line analysis, a defined device is placed close to the line to analyse the samples which may be occasionally or continuously extracted from the stream. Although the devices used in at-line analysis are mainly robust, they rely on standardized procedures and fixed parameter settings [24].

In-line analysers are simple sensors or measuring devices that are placed directly into a process stream. Therefore, there is no need to extract a sample from the process for examination. In-line process measurement performs the analysis either invasively by using a probe positioned in the process stream or non-invasively in which the probe does not have physical contact with the sample [25]. However, using in-line method, achieving a representative sample might be difficult since the measurements could be influenced by immediate process fluctuations. Temperature, pH, pressure, and flowrate are the usual process parameters which are measured in-line. On-line analysers are fully automated systems used to closely monitor the parameters that are critical in the production process. On-line methods have this ability to control the mixing processes by automatically changing the status of devices, such as valves, as part of their analysis sequence. Using an on-line measurement, continuously extracted samples from the process stream (by the means of a bypass) are transported to a specialized analyser and then returned to the process stream. This eliminates many preparation possibilities (i.e., all forms of destructive testing methods) and allows a large fraction of the product stream to be analysed [24].

Current research provides useful information on analytical methods for uniformity analysis of powder mixtures. Fast and accurate uniformity evaluation of powder blends is one of the challenges faced by many industries. This review article provides comprehensive background information on different powder mixing evaluation techniques and introduces the readers to the pros and cons of all the techniques in terms of cost, functionality, precision and operation conditions.

2. Wet techniques to assess powder blend uniformity

2.1. Ultra-Violet (UV)-visible absorbance spectrophotometry

By illuminating the sample with UV radiation and obtaining the absorbance, it is possible to estimate the concentration of a specimen. According to the Beer-Lambert law (Eq. 1), the absorbance information has a linear relationship with the concentration data [26, 27].

$$A = a(\lambda) \times b \times C \tag{1}$$

where A, b, C and $a(\lambda)$ are the measured absorbance, path length, specimen concentration and wavelength dependant absorptivity coefficient, respectively. Thus, UV-visible spectrophotometry is able to determine the concentration of the absorber in a solution based on Beer-Lambert law after selection of a proper wavelength. Quantifying the trend of the absorbance values versus different standard concentrations is necessary for the measurement of the unknown concentrations. Before spectral analysis of the unknown samples, spectrum background correction using a buffer blank is needed. According to Fig. 2-a, the unknown sample is placed between a light source and a photodetector. The intensity of the beam of UV-visible light, before and after passing the light through the sample, is then used to measure the unknown concentration [28].

Determination of the active ingredient content of powder mixture samples (especially in pharmaceutical products e.g. tablets and capsules) with UV-visible spectroscopy is a frequently useful technique [29, 30]. In a work done by Mendez et al. [20] pharmaceutical powder mixing was successfully evaluated in a V-blender during batch production using UV-visible spectrophotometry. The acetaminophen concentration of tablets, produced from samples from different regions of the blender at different times, was measured using UV-visible spectrophotometry (Agilent UV-VIS 8453E double-beam spectrophotometer at a wavelength of 244 *nm*). 3 samples of approximately 3.0 *g* were collected each time using a thief probe at three different locations (right, left and the bottom of blender). To perform quantitative determination, different standard solutions of acetaminophen were prepared to build a calibration curve.

Moreover, the UV-visible spectrophotometer is widely used as reference method for the determination of active ingredient during powder mixture as it is fast and simple method [31-33]. However, the disadvantages of this analytical method are as follow [34-36]:

-The main disadvantage of UV-visible spectrophotometry is that the absorbance spectra of soluble components are measured all together. Therefore, the separate measurement of component fractions within a mixture is not applicable in most cases using this technique.

-The impurities could influence the absorption spectra of the target component. Therefore, UV-visible spectrophotometry could not properly discriminate between the sample of interest and the contaminants absorbing at the same wavelength. Moreover, the detectors of the spectrophotometers are sensitive to the light. If any impurity in the sample reflects the light, an erroneous reading may be recorded by the detectors.

-Absorption values could be influenced by parameters such as temperature and pH leading to inaccurate result analysis.

-The sensitivity of a spectrophotometer is often inadequate at low concentrations.

2.1. HPLC (High-Performance Liquid Chromatography)

High-pressure liquid chromatography (HPLC) is a traditional off-line wet technique to separate, identify, and quantify the components in a mixture (Fig. 2-b). HPLC differs from the standard column chromatography method by the fact that it applies pressure to force the solution through the column, and therefore provides quicker, and more accurate results [37, 38]. As shown in Fig. 2-b, the solvent flows through a column with the help of a high pressure (up to 400 atm). The sample, injected to the mobile phase, is transported to the HPLC column for content determination as schematically shown in Fig. 2-b.

Fig. 2. (a) Schematic of UV-Visible spectrometer, (b) High-pressure liquid chromatography (with permission from University of Leeds).

The separation of components takes place in a stationary phase, fixed inside the HPLC column, because of difference in relative affinities of the constituents. Different retention times of the constituents in the outlet of HPLC column enables the estimation of different component fractions by a detector [39, 40]. A broad range of detectors such as UV/Vis, florescence (FL), Evaporative Light Scattering (ELSD) and Photo Diode Array (PDA) are available for the detection of different types of constituents in the mobile phase. The description of different detector types is beyond the scope of this article and the readers are referred to the additional sources on this topic [26, 37]. For the content analysis of the unknown samples, the standard solutions are first analysed by HPLC to obtain the calibration plot, from which it is possible to measure the chromatogram areas as a linear function of the concentrations of each constituent. After analysing the chromatogram of the unknown sample (Fig. 2-b), the concentration of each constituents could be specified [41].

For content uniformity testing of tablets, HPLC method was used by Walash et al. [42] for the determination of naftazone component. For this purpose, separation was performed using a Merck Hitachi L-7100 Chromatograph. A Nucleosil 100-5 phenyl column and a mobile phase comprising methanol-sodium dihydrogen phosphate mixture were used. Quantification of naftazone was performed by making a calibration curve obtained from different standards containing different concentrations of naftazone. Good correlation over the concentration range of 0.1-10.0 $\mu g/mL$ has been shown by this method with a lower detection and quantification limits of 0.032 and 0.096 $\mu g/mL$, respectively. Tanaka et al. [43] compared the efficiency of resonant acoustic mixing (RAM) technology for with ordinary mixing method for pharmaceutical blending process. The mixing of theophylline powder and lactose or magnesium oxide and lactose were carried out in a modified V-shaped mixing device and the APIs content uniformity in the mixture was quantified by HPLC method (LC-10vp series, Shimadzu). The API and lactose powders were mixed for 0.5 h at 30 rpm by ordinary method, and the powders were mixed for 0.01 h and 0.03 h at 100 G, 60 Hz by the resonant acoustic method. The coefficient of variation (CV) value of ordinary method was the largest and indicated non-uniformity. However, the CV values of resonant acoustic were smaller than ordinary mixing. The results showed that the resonant acoustic method could obtain content uniformity approximately 900 times more rapidly compared with ordinary methods [43].

Overall, as stated earlier UV-visible spectrophotometer method has its own limitation regarding the concentration measurement of each constituent in the mixture separately [42]. However, HPLC is frequently used for the separation, identification and quantification of different constituents in a mixture. Moreover, HPLC resolves the problem of the interference of active impurities and thus provides more accurate analysis compared to the UV-visible spectrophotometer method [44, 45]. Eraga et al. [46] analysed the content of ibuprofen ingredient, in ibuprofen tablets by UV-visible and HPLC method (Agilent Infinity 1260, Agilent Technologies Inc., USA). The standard samples was prepared by dissolving 100 mg of ibuprofen powder reference standard in a 100 mL volumetric flask with 0.1 mol/L NaOH solution. A 1 mL aliquot of the solution was further diluted to 100 mL to give the desired concentration. The main samples were prepared by dissolving of 100 mg of crushed ibuprofen tablets in water with similar procedure of standard sample preparation. The results showed that the HPLC method is more sensitive and reliable assay for ibuprofen detection compare to UV-visible spectroscopy and hence the HPLC technique suggested to be used for verification of the UV-visible method.

Beside several advantages of HPLC, there are several disadvantages for this analytical analysis technique. HPLC is time consuming as it requires two steps of 1-finding the optimum conditions (mobile phase composition, flowrate, injection volume and detector type) and 2-performing sample analysis at optimum conditions. Moreover, the complete package of HPLC facilities is expensive.

It should be noted that there are several issues with the above-mentioned traditional wet-based analytical methods. First, wet analytical methods are deemed tedious and time-consuming. Also, the material is lost by these methods because they the solid needs to be dissolved, hence, the studied material is not recoverable. Moreover, they are not classed as green method since they are wet-based techniques [47]. Therefore, other methods for analysing powder content are required which are briefly reviewed below.

3. Dry techniques to assess powder blend uniformity

3.1. Image analysis technique

With image processing of a captured photo from a powder mixture, it is possible to assess the uniformity of particles, providing that particles differ in colour. The 2D photo taken from the mixture of powders can be divided into several sections, where a component of interest can be quantitatively analysed using a potential image processing method. Then the fraction distribution of the desired component can be estimated in order to evaluate its homogeneity throughout the mixture [48, 49].

Rosas and Blanco [50] applied image processing technique to evaluate the mixing homogeneity of coloured sand (SiO_2) of different particle sizes in a blender. Two different set-ups were used to take the images during the mixing processes. Set-up 1 was based on at-line mode in which the samples were manually taken and photographed (using a Video meter Lab camera) and set-up 2 was based on a non-invasive image recording mode (Fig. 3-a). Different stages for the evaluation of the mixing quality of the captured photos are shown in Fig. 3-b. The quality of the raw image was first improved by some preliminary image pre-processing. After obtaining the segmented images using Matlab software, they were split into small subsections. Different mixing indices such as modified Lacey index, M_L (0 for totally segregated and 1 for totally random), modified Poole index, M_p (tends to unity in totally random images), homogeneity ratio defined by H_L and H_P % (100 for near-random and homogeneous mixture) were measured to investigate the quality of the powder mixtures. The homogeneity ratio was defined as the ratio of the mixing index (M_{image}) for an image and its randomized version (M_{random_image}). The mathematical correlation of different mixing indices has been presented in the study by Rosas and Blanco [50] in detail. Moreover, a review of different mixing indices used for the evaluation of powder mixing performance has been provided by Poux et al. [10].

Fig. 3. (a) Schematic of two setups applied for capturing images during mixing process and (b) different required steps for homogeneity assessment of images, (Reprinted from Rosas and Blanco [50]).

In a recent work, mixing of couscous particles of nearly spherical shape (with specific size ranges) in a continuous system has been assessed by on-line image-processing during steady and unsteady state regimes [51]. Using the on-line image-processing technique described by Ammarcha et al. [51], homogeneity of mixtures was evaluated by capturing all images of particles at the discharge of the continuous pilot-scale mixer (Fig. 4). The Charge Coupled Device (CCD, one pixel width-5000 pixels length) camera of the set-up was placed vertically with respect to the belt to film the passing mixture at different times. Each pixel represented a $60 \times 60\ \mu m^2$ surface on the belt which was much smaller than the size of each particle. The pictures were captured by grouping 200 consecutive one-pixel-width lines (500×200 pixel^2 image or $30 \times 1.2\ cm^2$ surface). Quality of the mixtures was evaluated by the concept of coefficient of variation obtained for the key ingredient.

There have been numerous reported works on this topic and Table 1 summarises some recent works based on image analysis technique for the evaluation of powder mixing performance.

Fig. 4. The combined mixer/image-processing for on-line monitoring of continuous mixing, (Reprinted from G. Ammarcha et al. [51]).

Table 1. Research works based on image analysis for powder blend uniformity evaluation.

In all the above-mentioned research studies, only the surfaces of mixtures were scanned for homogeneity characterisation. Slicing samples while preserving its properties, (e.g. using solidification of a mixture by a binder such as gelatin as solidifier and then refrigeration), could provide more content information from a discretized mixture. Measurement of the composition of a mixture, containing two coloured particles of granite stone, was performed by Realpe et al. [60] using a combination of slicing technique and image processing. Homogeneity of the mixture was assessed with image processing of the samples collected after slicing. After image processing of the captured pictures of the entire sliced samples (Fig. 5), mixing quality of the mixture could be evaluated. This technique could be beneficial to a broad range of industries such as metallurgy, pharmaceuticals, food processing and ceramics. Based on slicing technique, the internal structure of a mixture can be characterised off-line or at-line. In addition, the best binder should be investigated in such a way that it does not destroy the chemical structure while the internal physical properties are preserved.

Fig. 5. The top view of the sliced samples after solidification of a homogenised mixture, (Reprinted from A. Realpe et al. [60]).

Image analysis method is widely used for powder homogeneity evaluation due to its relative simplicity and low cost compared to the other techniques. However, this technique cannot be easily applied for the differentiation of components of similar colours. As the lighting conditions may not be always stable through the images, further background correction is also required for the analysis of the raw images. Moreover, unless slicing technique is used, image processing will provide only the surface properties of the mixture.

3.2. Assessment of powder blend uniformity by bulk particle properties

Bulk powder property can be a good indicator of powder homogeneity status during the mixing process. With determination of the bulk powder properties during blending, (e.g. monitoring pressure drop, conductivity, interaction charges or thermal behaviour), it could be possible to evaluate the mixing performance, which is briefly reviewed below.

3.2.1. Pressure drop method

Segregation of binary mixture of silica sand and silica gel was investigated by Olivieri et al. [61] in a Fluidization system. The pressure was monitored at different locations along the bed using pressure transducers to investigate the segregation pattern (Fig. 6-a). The plot of pressure gradient against the gas superficial velocity was used to discover the occurrence of segregation (Fig. 6-b). Velocity (U) between 2.2 and 9.1 *cm*/*s* demonstrated the bubble formation and the onset of segregation of sand particles at the bottom of the bed. The decreasing pattern of pressure gradient in upper region of the bed at this range of velocity, was reported to be as a result of the progressive accumulation of low density silica-gel particles in this region. A uniform pattern could be observed at U>9.1 cm/s.

In other work performed by Yudin et al. [62], different distributor configurations, such as perforated plate, circular edged slotted type (90°) and novel swirling type (45°), were used for the investigation of the mixing performance of a fluidized bed system using the pressure drop concept. The differential pressure readings across the column were logged using AZ Instrument™ 82012 differential digital manometer (resolution of ±1 mmH_2O and ±1.0% accuracy). Excellent particulate mixing was reported to be achieved by the novel swirling distributor without the need to apply mechanical rotation.

Fig. 6. (a) Schematic of fluidized bed equipped with pressure transducer (PT) and (b) pressure gradient versus gas superficial velocity at different heights of the bed, (Reprinted from Olivieri et al. [61]).

Using pressure drop information of a system, segregation patterns can be predicted only qualitatively and the technique could be potentially used to identify trend changes. Robust and precise quantitative analysis is needed for content analysis and mixing performance evaluation which will be described later.

3.2.2. Electrical conductivity method

Shenoy et al. [63] developed an at-line powder uniformity assessment method based on measuring the conductivity of powder samples. The effects of particle density, size and shape on the mixture uniformity in a lab-scale paddle mixer were investigated. The binary mixtures containing salt and other food seasoning powders were prepared and then the conductivity of different taken samples was measured by a conductivity meter instrument (SG78, Mettler Toledo). Using a conductivity calibration curve of salt obtained from analysis of different known standard concentrations, the unknown salt concentration of each sample could be determined.

In another study, Shenoy et al. [64] compared the image processing with salt conductivity method for the quality analysis of food powder mixtures. The powder mixtures were first located next to each other inside of the mixer, representing a fully segregated medium. Using a bent spoon (a kind of thief probe sampler), nine samples were extracted at five different mixing times. The extracted samples were then positioned in small containers (4 *cm* diameter and 1 *cm* height). Digital colour imaging (DCI) and salt conductivity method were used for measuring the salt concentration of each sample. It was demonstrated that the image processing technique could be a better option for mixing evaluation of multicomponent samples when the components had different colours. Using conductivity method, mixing performance of components could only be assessed in binary mixtures, containing conductive component (e.g. salt) and other non-conductive food components. For multicomponent food samples, only the mixing quality of salt would be determined. On the other hand, it was found that the image processing technique could not be a good indicator of mixing performance of components in the case of strongly segregated mixture of oregano and salt as it could not effectively detect the salt particles of samples which were sieved through the voids of oregano. In this case, conductivity method was reported to be a better candidate as it is volume sensitive.

In general, the conductivity method is a simple and inexpensive tool to study the powder mixture uniformity. This technique only needs a conductivity meter to measure the conductivity of samples in order to evaluate the mixing. The deficiency of this method is that it can only be applied for the differentiation of a component with high conductivity mixed with other low conductivity components.

3.2.3. Tribo-electrification method

Contact friction between particles causes a phenomenon called tribo-electrification or particle charging. The tribo-electrification phenomenon is due to particle-particle and/or particle-surface interactions, usually creating bi-polar charging, which allows the creation of attractive or repulsive forces between individual particles. Hao et al. [65] investigated the relationship between the electrostatic properties of different pharmaceutical powder formulations and the blending homogeneity in a V-blender. A Faraday Cup was used for the measurement of the electrostatic charge of particles (Fig. 7-a). The electrometer was zeroed after warming up when it was connected to the Faraday Cup. A glass beaker instead of metallic scoop/sampling thief was applied for transferring the samples to the container in order to mitigate the charge transfer from the operator and the container. Nearly 2 *g* of sample was enough to entirely coat the floor of the Faraday Cup.

The plot of particle charge versus blending time for six different samples taken from six different spots (three spots from each side) inside of the V-blender is shown in Fig. 7-b. The measured charge quantities were close to each other at 4 and 12 *min* (highlighted in red) indicative of a better uniformity of extracted powder samples under these conditions. Based on the observed results, existence of the cyclic nature of the charge change events which occurred with certain periodicity patterns upon continuous powder blending was reported.

Fig. 7. (a) A simple schematic of Faraday Cup and (b) charge versus blend time plotted for Blend 1 (200 *g* batch, 98.75% Avicel PH200, 0.50% Cab-o-sil, 0.75% Magnesium Stearate, Reprinted from Hao et al. [65]).

Measurement of the bulk electric charge of samples may offer a desirable and economical method for qualitatively assessing the powder mixing uniformity. However, it could be an unreliable tool for evaluating the mixing performance because the measurement is also affected by the variations of humidity, temperature and other environment factors [66].

3.2.4. Thermal analytical method

Effusivity has been used recently to evaluate the degree of homogeneity of powder mixtures by analysing the extracted samples of different locations of a mixer. This technique is based on evaluating the ability of powders to transfer heat, which depends on the particle size, shape, porosity and the composition of a mixture as well as the phase surrounding the particles. Effusivity has a proportional relationship with thermal conductivity (k), heat capacity (C_p) and density (ρ) of a substance as defined by Eq. 2. The sensor for this technique must be able to track the temperature changes within the powder samples in order to obtain the effusivity information [67].

$$Effusivity = \sqrt{k \rho C_P} \tag{2}$$

Leonard et al. [68] investigated the uniformity of pharmaceutical powders at-line by the effusivity technique. Experiments were carried out on three pharmaceutical binary mixtures (containing active and excipient ingredients) mixed in a V-blender. The sampling operation at different times was carried out using a thief probe after stopping the blender and collecting three samples of approximately 5 *g* from different corners of the blender. The concentration of active ingredient in the samples was estimated using standard calibration curves obtained from multiple blends of known active concentrations. Powder effusivity was measured using a BT-01™unit from Mathis Instruments (Fredericton, NB, Canada, Fig. 8-a), working based on the hot wire technology and tracking temperature changes within a sample during a given time interval. The uniformity patterns of active ingredient of different blends can be observed in Fig. 8-b. According to Fig. 8-b, all curves reached a plateau after a period between 6 and 8 *min*, indicating the end-point of mixing. The estimated error of this technique was reported to be ±3.4 % which was higher than that obtained from UV-visible spectrophotometry (±0.7 %). The work reports that more accurate analysis can be performed by UV-visible spectrophotometry, however, it is destructive, time consuming and not applicable as an in-line measurement mode. On the other hand, effusivity technique could potentially be used as an effective and fast tool for determining the end-point time of powder blending processes.

Fig. 8. (a) Schematic of BT-01™ unit and (b) evaluation of Acetaminophen homogeneity at three sampling positions of a V-blender using effusivity measurement, (Reprinted from Leonard et al. [68]).

Differential Scanning Calorimetry (DSC) is another method for the evaluation of powder uniformity which works based on heat transfer phenomena. This method uses enthalpy values to predict the sample content and offers a simple and cost-effective means of monitoring powder blending [69]. Bharvada et al. [70] evaluated the mixing of binary pharmaceutical mixtures, containing Microcrystalline cellulose (MCC) and active component of Atenolol, in a high shear mixer using the DSC technique. For the analysis of the mixing performance, different samples (equal to 3 × the quantity of drug) were extracted from different locations of the mixer (top, middle and bottom) using a sampling thief. The enthalpy of samples was measured by an Indium calibrated Auto DSC (TA Instruments, USA). The relative standard deviation (*RSD)* of unknown samples (Figs. 9-a and 9-b) extracted from several positions of the blender was estimated using standard calibration curve, obtained from analysing several known active component fractions with known enthalpies. The *RSD* was found to be low after 15 *min*, indicating the optimum time of mixing for the binary system of MCC-Atenolol blend. From the comparison of the results of DSC technique with HPLC method, it was concluded that the relative standard deviation measured by DSC was higher than that obtained using HPLC for lower levels of drug, i.e. 0.5%, 1% and 2%. However, the results of DSC and HPLC techniques were nearly similar for the concentrations above 5%.

Fig. 9. (a) Average enthalpy changes of top, middle and bottom samples in the mixer and (b) % *RSD* of top, middle and bottom samples of microcrystalline cellulose-Atenolol blend at different time points, (Reprinted from Bharvada et al. [70]).

The above-mentioned methods based on thermal characterisation are convenient and simple for the evaluation of powder uniformity. However, a sampling operation, using thief probe is needed for the extraction and analysis of thermal behaviour of samples which might disturb the powder bed, and therefore results may be biased [10, 15]. Although the uniformity assessment results derived from thermal characterisation methods shown earlier seem to be reliable and accurate, these methods should be applied to more powder systems with complex thermal behaviour.

3.3. Tomographic techniques

There are several tomographic techniques [71] such as X-ray, positron emission particle tracking, electrical capacitance and magnetic resonance imaging, used for the evaluation of powder blend uniformity which are reviewed in this section.

3.3.1. X-ray microtomographic method

X-ray computed microtomography (μCT) is a non-invasive technique performed for the evaluation of powder homogeneity which could provide high resolution images (typically 50 microns or less) [72]. By projecting an X-ray beam through the material and the measurement of the energy debilitation of the beam received on a detector, a three-dimensional structure of an object could be constructed. Liu et al. [73] used X-ray microtomography to evaluate the mixing and segregation of a binary system containing spherical and non-spherical particles at different times of vibration inside a cylindrical container. Since the size of the container (9 *mm* in diameter and 28 *mm* in height) was too large for the image acquisition process, different samples at the upper, middle and lower levels of the cylindrical container were exposed to the X-ray light beam (Fig. 10-a) and the total projected images were reconstructed at different vibration times (Fig. 10-b). The pixel size, the exposure time and the sample-to-detector distance were 13.0 μm, 1.0 *s* and 25.0 *cm*, respectively. The uniformity of mixture was analysed using a numerical index, S', based on the sphericity of particles, estimated by following equations:

$$\sigma^2 = \frac{\sum_{i=1}^{N_l}(s_i - \bar{s})^2}{(N_l - 1)} \quad (3)$$

$$\bar{s} = \frac{\sum_{i=1}^{N_P} s_i}{N_p} \quad (4)$$

$$S' = \frac{\sigma}{\bar{s}} \quad (5)$$

where $\bar{s}$, Np, s_i and N_l are the mean sphericity measured over the totality of the particles in all three levels of the container, particles in the upper, middle and lower levels in total, the i^th^ value of s which represents a sphericity of the particle and particles in one level, respectively.

Components were displayed with different colours depending on the sphericity of the particles. The increased degree of coincidence of the normalized frequency distributions with vibration time obtained for the upper, middle and lower levels indicated a better uniformity at higher vibration times (Fig. 10-c).

Fig. 10. (a) The schematic of mixing process, (b) images taken at different times of rotation and (c) evaluation of the mixing performance by normalized frequency distribution, (Reprinted from Liu et al. [73]).

Surface imaging tools such as Scanning Electron Microscope (SEM) are only able to scan the outer surface of objects and therefore they cannot be applied for full-scale evaluation of powder mixtures. On the other hand, μCT has a great potential for deep understanding of the structural properties of particulate materials [74, 75]. Precise data analysis could be provided from rendered high resolution images using this technique. However, material with similar structural properties cannot be easily differentiated using this technique. Also, this method is an expensive tool for the evaluation of powder homogeneity.

3.3.2. Positron emission particle tracking (PEPT) method

Positron emission particle tracking tomography is an imaging technique that produces a three-dimensional image of a process by detecting pairs of gamma rays emitted by a positron-emitting radio nuclide (tracer) into the system [76-79]. The spatial accuracy in a range of 0.5 *mm* (observed at 500 times per second) was reported for particle velocity of 1 *m*/s [80]. The accuracy reduces as particle velocity is increased because the particle moves further and therefore more detectors are needed to spot the tracer [80]. Also, the accuracy of this method depends on the measurement conditions, specifically the mass of material between the tracer particle and the detectors. The size and density of the tracer are considered to be approximately the same as the components inside the mixer. Therefore, it would be possible to assume that the movement of the tracer closely follows the components in the mixer. Marigo et al. [81] studied the mixing behaviour of glass spheres inside a cylindrical Turbula mixer with the use of PEPT technique. Glass particle tracer as well as two detectors for tracking the gamma rays of the tracer were applied. By the measurement of axial and radial diffusion of the tracer (Eqs. 6 and 7, respectively), the mixing efficiency was evaluated for different operating conditions in axial and radial directions (Fig. 11-a).

$$D_x = \frac{1}{N'-1}\sum_{k=1}^{N'-1}\frac{(x^{k+1}-x^k)^2}{(t^{k+1}-t^k)} \qquad 6$$

$$D_r = \frac{1}{N'-1}\sum_{k=1}^{N'-1}\frac{(r^{k+1}-r^k)^2}{(t^{k+1}-t^k)} \quad 7$$

where x^k and x^{k+1}, N', r^k and r^{k+1} are the axial positions of the particle at time t^k and at time t^{k+1}, the total shaft rotation and the radial positions of the particle at time t^k and at time t^{k+1}, respectively.

The tracer motion was further discussed by occupancy concept which is defined as the ratio of time that the tracer spends at a given position to the total tracking time. By increasing the speed of cylindrical Turbula mixer up to 46 *rpm*, a clear core-shell pattern was observed in the transverse and axial direction (Fig. 11-b). This event represented the tendency of the tracer particle to stay in two core regions of the bed in the axial direction which hindered the tracer particle to cross the middle point. This core-shell pattern represented the inadequate mixing operation, leading to a decrease in the mixing efficiency in the axial direction.

Fig. 11. (a) Comparison of dispersion coefficients, D_x and D_r, as a function of rotation speed and (b) occupancy plots for 20 *min* measurement time, (Reprinted from Marigo et al. [81]).

Gundogdu [82] described a technique based on a clustering method to track multiple particles rather than single tracer particle, enabling exploration of more comparative information about the mixing in a system. The study of Gundogdu offers a unique solution to track more than one particle. He found that ^{18}F radioactive particles provided better results than ^{22}Na particles. All experiments of Gundogdu were carried out in open air and calculations were performed in off-line mode. It should be noted here that more intensive investigation of this method is needed due to the complexity of its procedure [82].

PEPT is a non-invasive technique for evaluating the flow processes by tracking the motion of a radioactive tracer particle. This method allows looking through opaque systems without interfering with flow [83]. However, erroneous locations may also be calculated using this technique due to scattering of gamma rays. In addition, in order to obtain reliable data long run experiments have to be carried out, allowing the tracer (s) occurrence in different regions of a mixer, except in the stagnant sections [84].

3.3.3. Electrical capacitance tomography

Electrical capacitance tomography (ECT) provides a non-intrusive cross-sectional view of a stream which can be obtained by the measurement of variations in dielectric properties (relative permittivity) of the materials inside the vessel. The main advantage of this technique is that it could provide a cross-sectional view of a stream, containing liquid, solid and/or gas, in a non-intrusive way. However, as compared to X-ray, γ-ray, as well as Magnetic Resonance Imaging (MRI), this low-resolution technique (spatial resolution typically 3-10 % of a pipe diameter) has limited application to powder mixtures that require an analysis at very fine scale. Ehrhardt et al. [85] used an electrical capacitance sensor consisting of two copper electrodes placed around a glass tube to assess the segregation problems of discharging silicon carbide (SiC) and sugar mixture (sugar at the bottom and SiC at the top) through two funnels (Fig. 12-a). The sensor was connected to a capacitance meter and further to a computer through an analogue/digital converter to estimate the capacity of particles. It is found that in the lower funnel, silicon carbide was mixed with sugar at the beginning of the experiment, whereas segregation was observed after a while (Fig. 12-b). This was reported to be as a result of density segregation of silicon carbide.

Fig. 12. (a) Schematic of the experimental rig comprising the initial mixture (1), vibrating channel (2), upper funnel (3), sensors (4), static mixer (5), lower funnel (6), belt conveyor (7) and capacimeter (8), (b) discharge profiles through a funnel, (Reprinted from Ehrhardt et al. [85]).

In new research done by Huang et al. [86], a new measurement method for the mixing of binary mixtures was developed based on capacitance probe in a bubbling fluidized bed. A capacitance measurement instrument (MTI Accumeasure) was used to measure the signals of capacitance probes from different measurement points of the fluidized bed (Fig. 13-a). A linear relationship between the signal of the probe and fraction distribution of solids in binary mixtures was considered (Eqs. 8-10).

$$C_1 + C_2 + C_a = 1 \tag{8}$$

$$C_1 * v_1 + C_2 * v_2 + C_a * v_a = v \tag{9}$$

$$C_1 = \frac{v}{v_1 - v_2} + \frac{v_2(1 - C_a) - C_a v_a}{v_1 - v_2} \tag{10}$$

where v, v_1, v_2, v_a, C_1, C_2 and C_a are the measured probe voltage signal, voltage signal corresponding to pure substance of solid 1, solid 2, air, the volume fraction of solid 1, solid 2 and air in the mixtures, respectively.

The fraction of quartz sand particles at different bed heights of a binary mixture of polypropylene plastic and quartz particles is shown in Fig. 13-b. It can be observed that the fraction of quartz in the lower part of fluidized bed (30 *cm*<) is high, while a decrease at heights above 30 *cm* is observed. A successful segregation measurement of binary mixture in the fluidized bed using capacitance probe was confirmed using this method.

Fig. 13. (a) Schematic of fluidization experiment and the structure of capacitance probe and (b) fraction distribution of sand in polypropylene plastic and quartz sand mixture, (Reprinted from Huang et al. [86]).

ECT shows great potential in many harsh conditions such as high-pressure or high temperature. However, this technique has a relatively low spatial resolution. Moreover, it is only applicable for the materials with noticeable variations in dielectric properties.

3.3.4. Magnetic resonance imaging tomography

Magnetic resonance imaging (MRI) is a tomography system that provides a non-invasive 3D images of a mixture using strong magnetic field generated by the surrounding powerful magnets [87]. The signal intensity of one voxel in MRI is proportional to the atomic nuclei number of observable elements such as hydrogen, phosphorus or fluorine. Hardy et al. [88] studied the mixing performance of oil-filled melamine microcapsules (hence visible to MRI) and solid melamine spheres in a cylindrical container using a MRI method. A tomographic system (Bruker Avance 200 SWB, Bruker Biospin MRI GmbH, Ettlingen, Germany) was used to track the visible particle signal intensity. A 1 cm^3 mixture volume was imaged with an isotropic spatial resolution of 235 μm. The effectiveness of the MRI technique for quantitative characterization of fine powder mixtures (size range of about 10 μm) has been shown in this article. Three orthogonal slices through the 3D mixture data set at each mixing step are shown in Fig. 14.

Bright and dark regions represent the presence of MRI active particles and non-visible particles, respectively. It is evident from Fig. 14 that the uniformity was achieved at higher time steps, referring to the end-point of mixing identified using the MIR method.

Fig. 14. MRI slices through a cylindrical powder sample at different time steps, (Reprinted from Hardy et al. [88]).

The limitation of MRI method lies in the fact that the particles mainly need to be coated by substances, such as oil, to be visible by MRI. Coating of particles may change the powder flow characteristic which could influence their mixing behaviour [89-91]. Also, the spatial resolution is less than the μCT method [92]. A summary of research work based on tomographic techniques for powder homogeneity assessment is presented in Table 2.

Table 2. Summary of different tomographic techniques for powder mixing assessment.

3.4. Spectroscopic techniques

Spectroscopic techniques have already found a wide range of applications in industrial sectors [91]. In particular, component composition of samples could be determined using their spectral information and used to evaluate the mixing performance. In this regard, different spectroscopic methods along with their functionalities are explained in the following sections.

3.4.1. Near-infrared spectroscopy

NIR spectroscopy is a molecular vibrational spectroscopic method for the detection of vibrational transitions in the molecules that can be performed either by diffuse reflectance or transmission mode. The intensity ratio of the scattered light from the sample compared to the light reflected from a reference surface can be measured by the diffuse reflectance mode. On the other hand, decrease by radiation intensity can be detected by the transmission mode when radiation passes through the sample [92].

There are numerous research works investigating the powder uniformity using Near-Infrared (NIR) spectroscopy (Table 3).

Table 3. Current researches investigating the powder blend uniformity using NIR system.

In order to monitor the mixing of powders, a segregation tester device was developed by Johanson [116] which works based on a relationship between the mixture NIR spectral intensity and the spectral intensity of pure components. Based on a similar concept, Asachi et al. [117] and Oka et al. [118] evaluated the mixing performance of powders, where component fractions are determined by minimization of the difference between the computed intensity curve of the mixture (Eq. 11) and one measured using a spectroscopy tool as shown in Eq. 12 [117]. The distribution of component fractions through the mixture could then be used for the evaluation of powder mixing uniformity.

$$FS_{mix}(\lambda) = \sum_{i=1}^{n_{comp}} (x_i . FS_i(\lambda)) \tag{11}$$

$$Error = \sum_{k=1}^{n_{wave}} (FS_{mix}(\lambda_k) - F_{mix}(\lambda_k))^2 \tag{12}$$

where $FS_{mix}(\lambda)$, $FS_i(\lambda)$ and x_i are average intensity of the mixture, average intensity of pure components and fraction of components, respectively.

Asachi et al. [117] investigated the effect of using different pre-processing methods on the measured component fractions according to the above-mentioned approach; scatter correction and the combined smoothing-derivatives. The second derivative of the smoothing technique of Norris-Williams method was reported to be the best pre-processing method for the quantification of low content level enzyme granules (1.85 % w/w) in the mixture of washing powders; the percentage error for the quantification of segregation of low content level enzyme in a heap of powder mixtures was reported to be around 10 %.

Concentration profiles of three types of bird seed in a pile of powders, estimated using the segregation tester, are shown in Fig. 15-a. Spectra of the pure components and those obtained for the mixture are shown in Fig. 15-b. Good agreement between the actual values and the predicted values is observed in Fig. 15-b. The smallest representative size (view port) of each sample, was deduced by plotting the segregation intensity factors as a function of view port size (Fig. 15-c). According to Fig. 15-c, a view port size of about 4500 μm was suitable for sand with an average particle size of 1500 μm. The expected error of this method was reported to be within 7% and 0.5% for a badly segregating and moderately segregating materials, respectively. Moreover, suitable range of particle size for this device was reported to be between up to 3 *mm*.

Fig. 15. (a) Concentration profiles of segregation for a mixture of three bird seeds and (b) spectra of pure components and mixture and (c) segregation intensity as a function of viewport size, (Reprinted from Johanson [116]).

Koller et al. [119] applied a FT-NIR spectroscopy with a fiber optical reflection probe in a four- bladed mixer to assess the mixing process in pharmaceutical powder mixtures. The NIR spectra were recorded using a PerkinElmer FT-NIR400 Spectrometer. A penetration depth of approximately 0.3-0.5 *mm* and a spot diameter of 4 *mm* (sampling volume of approximately 6 mm^3) was reported for the studied probe. Fiber optical probe of the spectrometer was introduced in direct contact with the powder bed during mixing process (Fig. 16-a). The pure and mixture spectra were analysed by Partial Least Squares Regression (PLSR) to estimate the concentration change in the mixtures (Fig. 16-b). It is shown that locating a NIR probe in powder beds is a suitable method to determine the end-point time of blending. The Root-Mean-Square Error of Prediction (RMSEP) was reported to be in the order of 2 to 3 % for the API content.

Fig. 16. (a) Experimental of an in-line NIR setup with a four-bladed mixer connected to a controllable mixing device and (b) blending plots for the mixer, light grey represents acetyl salicylic acid (ASA) and dark grey shows α-lactose Monohydrate, (Reprinted from Koller et al. [119]).

Other configurations of NIR set-ups have also been applied to monitor greater quantities of samples. By placing several NIR probes at several positions of a blend, it is possible to monitor the entire blend [32, 120]. Scheibelhofer et al. [121] applied multiple NIR probes, connected to a Fourier-transform NIR spectrometer, to quasi-simultaneously investigate the pharmaceutical blend uniformity at multiple positions (Fig. 17-a). In contrast to thief sampling, the samples are analysed here by applying probes. In this work, it is shown that the size of sample volume (defined as the number of particles contained in the sample) was dependent on the particle speed in front of the sensor window and the number of accumulated spectra (Fig. 17-b). The measured volume, at optimum case, was reported to be about 16 mm^3 which was less than the final dosage form (75 mm^3). Standard deviation of the model predictions was estimated to be about ± 5% using this set-up. In a recent work, the potential of NIR spectroscopy for continuous monitoring of powder flow was demonstrated by Alam et al. [122]. The information from the bulk phase of the powder stream could be obtained using transmission NIR spectroscopy (NIR spectrometer with a diode array detector). According to the analysis, the proposed NIR device could detect the NIR signal intensity of powder beds up to 5 *mm* in thickness. The analysed volume of each sample using this transmission NIR method was estimated to be around 0.25 mm^3. Quantitative determination of API concentration in the developed continuous stream of powder was carried out at different process parameters (such as powder flow rate and tube angle). A schematic of on-line monitoring of continuous stream using transmission NIR is illustrated in Fig. 17-c. As shown in Fig. 17-c, a tube connected to the powder feeder was used to deliver the samples to the NIR spectrometer, where the spectra could be recorded in a non-contact manner.

Fig. 17. (a) Schematic of multi-probe spectroscopy setup, (b) dependence of the sample volume size to the number of accumulated spectra and the moving speed in front of the sensor window (f = 1 is the tip speed of the blade, f = 0.5 is half of this speed) and (c) continuous blend monitoring of powder streams using transmission NIR, (Reprinted from Scheibelhofer et al. [121] and Reprinted from Alam et al. [122]).

NIR offers a fast chemical imaging of multicomponent mixtures and continuous monitoring of samples at different modes of at-line, in-line and/or on-line [123]. However, it is difficult to obtain a very high-resolution visualization to the internal field of particulate systems using this method. Furthermore, overlapped spectra of different components could pose difficulty and challenge when using the NIR technique to assess homogeneity of a mixture.

3.4.2. Raman spectroscopy

The irradiation of materials cause different phenomena including scattering, absorption and fluorescence (Fig. 17). The Raman effect is a scattering process that alters the frequency of an incoming monochromatic light beam, mainly from a laser in the visible, Near-Infrared, or near Ultraviolet range [124].

Fig. 18. IR and NIR absorption, the Raman effect and fluorescence, (Reprinted from De Beer et al. [25]).

Allan et al. [125] used an on-line Kaiser Raman spectrometer with a non-contact optic to obtain the spectra of powder mixture in a high shear convective blender (Fig. 19-a). A sampling depth of over 3.5 *mm* and an estimated sampling volume of about 11.095 cm^3 (equated to a mass of 4.99 *g*) was reported for the measurement of aspirin in Avicel using this system. The mixing end-point of different amounts of aspirin and Avicel was investigated using this technique (Fig. 19-b). As shown in Fig. 19-b, by increasing the amount of aspirin, more time was needed to achieve a homogeneous state. The detection limit of aspirin in Avicel using the proposed Raman system (2nd derivative at 1606 cm^{-1}) was reported to be around 1.1 % (w/w).

Fig. 19. (a) Schematic of Raman probe and sample set-up and (b) Raman probe mixing profiles at 1606 cm^{-1} for the case of the addition of different amounts of aspirin to Avicel, (Reprinted from Allan et al. [125]).

In a recent work, Wang et al. [126] developed a custom-designed macro-Raman based system for homogeneity analysis of multi-component bulk of pharmaceutical powders (Fig. 20-a). The studied spectroscopy system was equipped with a motorized translational sample stage (Fig. 20-a). For the quantitative analysis of component fraction, a correlation based on spectral information was applied as follows:

$$\frac{Y_i}{Y_j} = c_j^i . \frac{I_i}{I_j} \qquad (13)$$

where *I* and *Y* are the spectral intensity of the component i or j at all wavenumbers to the measured raw spectrum of the mixture and the mass fraction of components, respectively.

In the first part of the analysis, a direct relationship between the errors of the measured compositions and the analysed sample volume and sampling methods was demonstrated. Larger sample volume scanning, across cavity or groove (Fig. 20-b), was shown to be more suitable for bulk composition analysis of inhomogeneous samples. Therefore, more representative bulk compositions of inhomogeneous samples were analysed by the cavity or groove scanning methods. A large error was reported for the single spot sampling method (sample volume of 0.4 μL) which was mostly due to its relatively smaller sample volume. Binary mixtures of leucine and mannitol with equal masses were mixed for different times using a wrist action shaking machine. From analysis of several samples at different times, a cumulative distribution of mass fraction of leucine was obtained as shown in (Fig. 20-c). According to Fig. 20-c, mixing deteriorates in the binary mixture of leucine and mannitol during blending (as standard deviation of the measurements was increased by time).

Fig. 20. (a) Dispersive macro-Raman Set-up, (b) different sampling methods: single spot (I), scanning across the cavity (II), scanning along the groove (III) and (c) cumulative distributions of the measured leucine mass fraction during mechanical mixing, (Reprinted from Wang et al. [126]).

Raman imaging has less overlapped spectra and higher spatial resolution as compared to the NIR and therefore it has a better sensitivity to detect minor components [127, 128]. Thus, Raman eliminates the limitation of NIR in which the overlapped spectra make it difficult to perform low dose quantitative analysis. However, this technique is more expensive than NIR. In addition, substantial interferences in Raman spectra can be produced by fluorescence when the molecule is excited to an elevated state [25, 47, 129]. For the elimination of the fluorescence contribution, some researchers proposed stimulated Raman scattering (SRS) [25, 130, 131]. The advantage of SRS is that it removes the non-resonant background via heterodyne detection. Therefore, SRS is free of non-resonant background and fluorescence contribution and it allows selective imaging of the molecules.

3.4.3. Acoustic emission spectrometry

The impact of particles on the inner surface of a vessel, which generates the acoustic emission, can be used to non-invasively monitor the particulate process. The attachment of a transducer to the outside of a vessel is the most common method to detect acoustic emission of particles. It is also possible to estimate the size of particles from the acoustic emission signals created from particle–particle collisions. Allan et al. [132] investigated the blend process monitoring of aspirin or Avicel added to Avicel particles in a scaled-down convective mixer with the use of powder acoustic emission (AE). Mixing profiles which were produced from the measurement of AE spectra in this system, are represented in Fig. 21-a. No change could be observed in the mixing profile when Avicel was added to Avicel particles. However, the AE signal increases in the case of the addition of aspirin, and after a while it reaches a plateau as the mixture becomes homogeneous (about 700 *s*). In another part of this study, the effect of impeller speed on the AE response was investigated. It was found that at low impeller speeds (<50 *rpm*), the movement and velocity of powders near the glass wall was not sufficient, thus a small acoustic signal was produced.

Following the previous research, Allan et al. [125] carried out a comparison between different techniques of NIR, acoustic emission and Raman spectroscopy for obtaining mixing profiles. The end-point identified for the blending process as well as the trends of the mixing profiles were similar for the three techniques (Fig. 21-b). However, the detection limit for aspirin in Avicel using the acoustic emission (AE) system was reported to be around 5.2 % (w/w) which was poorer than that reported for the Raman and NIR systems.

Fig. 21. (a) Acoustic emission mixing profiles and (b) mixing profiles for the addition of 30 *g* aspirin to 75 *g* Avicel, (Reprinted from Allan et al. [125, 132]).

Acoustic emission has the advantage of being a non-invasive monitoring method for powder mixing. Unlike many techniques, such as NIR, which needs an optically transparent window in the process vessel, this method is able to collect the spectral information of blends behind any type of wall material. Also, the cost of an AE measurement system is less than NIR spectroscopy. However, some authors [125, 132] reported that this method would only be representative for powder composition at the interface rather than in the bulk material as AE spectra only could be obtained by the collisions of particles with the vessel wall [125, 132]. The depth information for AE spectrometry is reported to be less than other spectroscopic techniques such as NIR (typically 2-3 *mm*). Moreover, the sensitivity of AE is found to be poorer than NIR and Raman spectroscopy.

3.4.4. Fluorescence spectroscopy

Materials that absorb ultraviolet or visible light energy, may dissipate a part of the energy as heat or electromagnetic radiation. The latter phenomenon is called fluorescence. The fluorescence detection of materials can be useful to study the behaviour of processes and therefore is a potential tool for the assessment of content blend uniformity [133, 134]. Domike et al. [135] used a light induced fluorescence (LIF) instrument to evaluate the total content of fluorescent active pharmaceutical ingredient (API) in tablets. Ten tablets from three batches containing different weights of triamterene have been tested using this technique and the results were compared with those obtained by UV-visible spectrophotometry. The position of tablet relative to the LIF instrument is shown in Fig. 22-a. The concentration of the API of tablets was obtained by plotting the calibration curve of LIF signal against different standard API concentrations. Figure 22-b shows a relatively good agreement between the results of fluorescence spectroscopy and UV-visible spectrophotometry analysis. The Root Mean Standard Error of Prediction (RMSEP) for LIF was reported to be in the range of 4.40-7.93%.

Fig. 22. (a) LIF instrument and (b) triamterene concentration obtained using LIF and UV analysis, (Reprinted from Domike et al. [135]).

In another study, Karumanchi et al. [136] used a LIF sensor (with a sample volume of approximately 0.117 cm^3) to evaluate and monitor the blend homogeneity of fluorescent API. For this purpose, the data obtained from LIF sensor placed on the surface of collected samples containing fluorescent API was analysed. A stainless-steel grain type sampling thief was used for extracting the samples. The excitation wavelength of the fluorescent API was reported to be around 330-360 *nm*. Five LIF measurements were made on each sample. Using fluorescence reference standards, the calibration of LIF sensor to estimate the final API concentration was performed. The results showed that the blend met the $\%RSD \leq 4\%$ criterion at 2-20 *min*, indicating to an acceptable mixing status during this blending interval. A linear relationship

($R^2 = 0.97$, $p < 0.0001$) was observed between LIF %RSD and HPLC %RSD, suggesting that LIF can be successfully used to qualitatively evaluate the blend homogeneity.

Sensitivity of fluorescence is greater than absorption spectroscopic methods because it uses both excitation and emission wavelengths. It is available with relatively low cost and it is fast and sensitive to differentiate active content at low concentrations. However, fluorescence intensity is sensitive to fluctuations in pH and temperature. Also, the applicability of this technique depends on the strength of fluorescence of the component to be investigated relative to the fluorescence of other components within the mixture.

4. Conclusions

To obtain a high-end product quality, mixture of powders should be made with high content uniformity to reduce powder segregation and product failure. Numerous uniformity assessment methods for particulate systems have been developed and studied over the last few decades. In this study, different techniques for the assessment of blend uniformity have been examined. Spectroscopic approaches such as NIR and Raman have been broadly used for the assessment of powder mixture uniformity. These techniques attracted more attention due to the fact that the uniformity of several components can be monitored either at-line, in-line and/or on-line using these techniques. However, using tomography systems or methods based on particle properties, such as conductivity, one or two ingredients could be monitored usually in an at-line mode. Among different spectroscopic tools, Raman and fluorescence showed a high sensitivity to detect minor components, therefore they can be applied for the evaluation of powder uniformity with higher accuracy. However, NIR spectroscopy is more commonly used for the evaluation of powder homogeneity due to its relatively low cost as compared to other spectroscopic instruments. In general, the suitable technique must be chosen according to the application, material and device specifications, budget as well as the required precision and sensitivity. The advantages and disadvantages of all the reviewed techniques are briefly summarised in Table 4.

Table 4. Powder uniformity assessment techniques with their advantages and disadvantages.

In certain circumstances, different techniques could lead to false conclusions. For example, wrong choice of dilution technique may lead to inaccurate results obtained by HPLC and/or UV-visible absorbance spectrophotometry [69, 137]. Improper light condition, dirty camera lenses, a low-resolution camera and unreliable image-processing softwares could influence the accuracy and reliability of the image analysis. For instance, Abdelrahman et al. [138] evaluated the flow detection of particles using optical imaging. It was shown that changing the camera focus on the point of interest could affect the accuracy of the particle detection. In spectroscopic techniques, scanning cannot be achieved properly when a sticky lump of powders adheres to an optical sensor during the process. In addition, the efficiency of spectral acquisition and the related data analysis is highly dependent on the distance of the probe from the powder mixture. For example, 3 *mm* is reported to be the most efficient distance for the MicroNIR1700® probe in the related study of Asachi et al. [117]. Other factors which influence the light absorption such as porosity, particle morphology, particle size distribution and powder layer thickness must be precisely considered during spectral analysis [139]. Environmental conditions, such as humidity and temperature, must also be taken into consideration for an accurate result analysis in different techniques such as NIR spectroscopy, tribo-electrification and electrical conductivity [140-143].

Nomenclature

AE	Acoustic emission
API	Active pharmaceutical ingredient
ASA	Acetyl salicylic acid
CCD	Charge coupled device
CV	Coefficient of variation
DSC	Differential Scanning Calorimetry
ECT	Electrical capacitance tomography
FT	Fourier-transform
HPLC	High-Performance Liquid Chromatography
LIF	Light induced fluorescence
MCC	Microcrystalline cellulose
MRI	Magnetic resonance imaging
NIR	Near-Infrared

PEPT	Positron emission particle tracking
PLSR	Partial least squares regression
PT	Pressure transducer
RAM	Resonant acoustic mixing
RSC	Royal society of chemistry
RSD	Relative standard deviation
SEM	Scanning electron microscope
SiC	Silicon carbide
SRS	Stimulated Raman scattering
U	Velocity
UV	Ultra-Violet
μCT	X-ray computed microtomography

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Figure

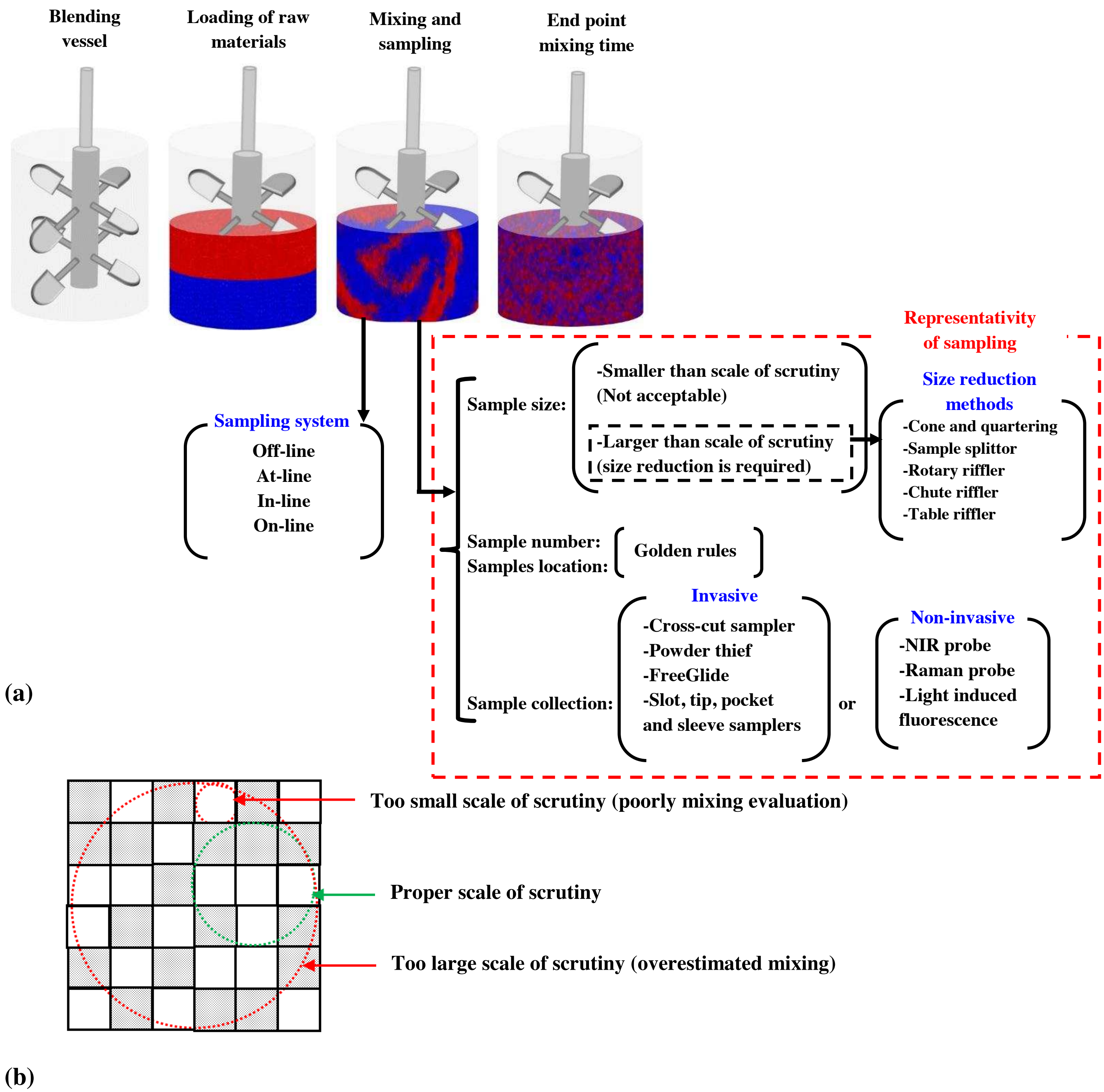
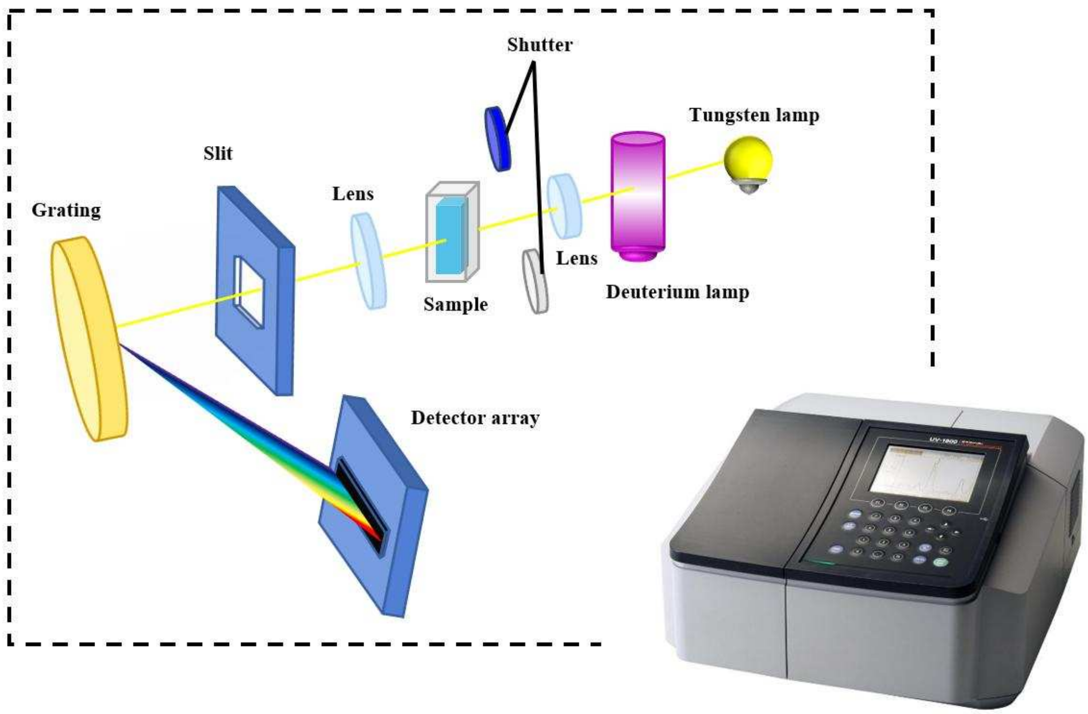


Fig. 1. (a) A general framework of sampling in powder mixing processes, (b) effect of the scale of scrutiny on mixing evaluation.



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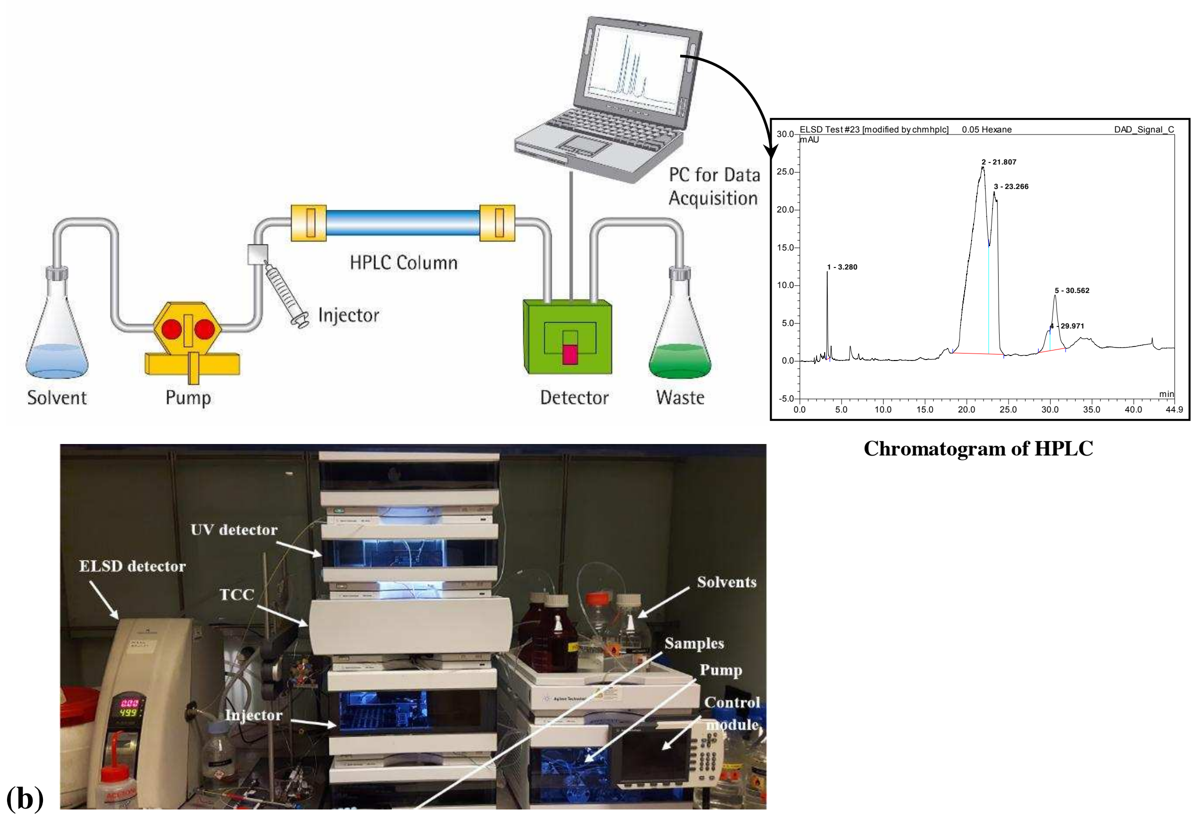
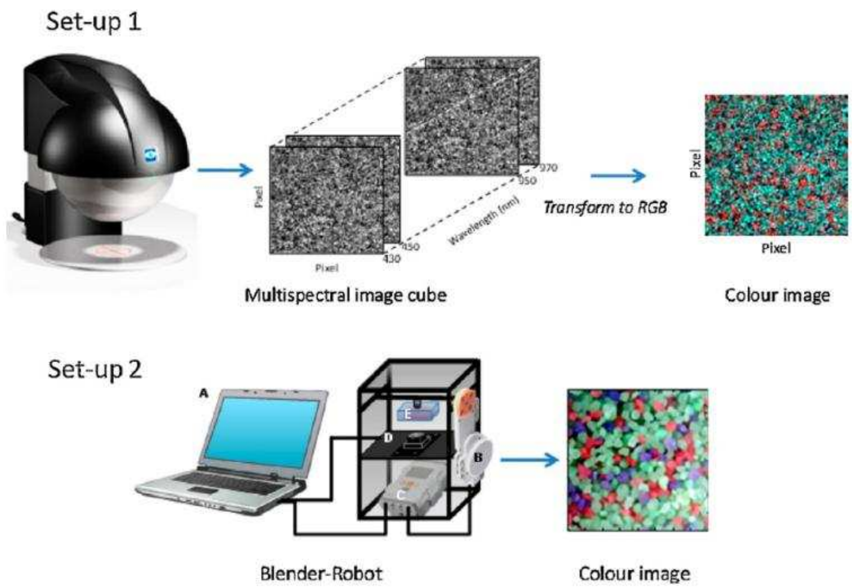


(b)

Fig. 2. (a) Schematic of UV-Visible spectrometer, (b) High-pressure liquid chromatography (with permission from University of Leeds).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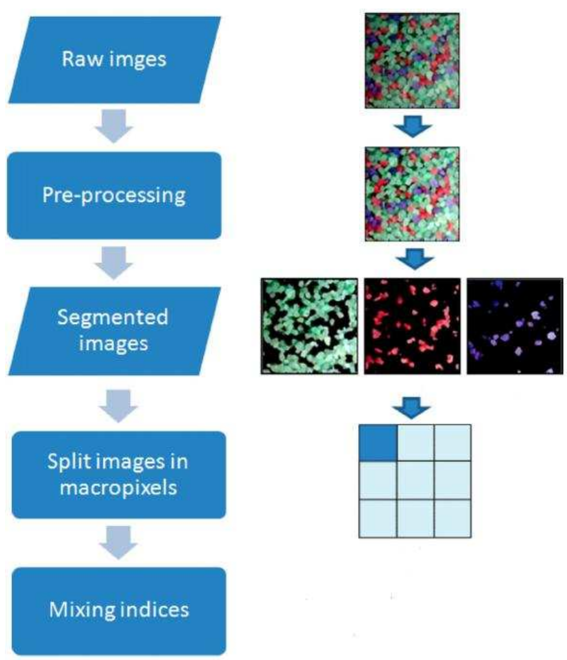
Colour image

(a)


Raw imges
Pre-processing
Segmented images
Split images in macropixels
Mixing indices

(b)

Fig. 3. (a) Schematic of two setups applied for capturing images during mixing process and (b) different required steps for homogeneity assessment of images, (Reprinted from Rosas and Blanco [50]).

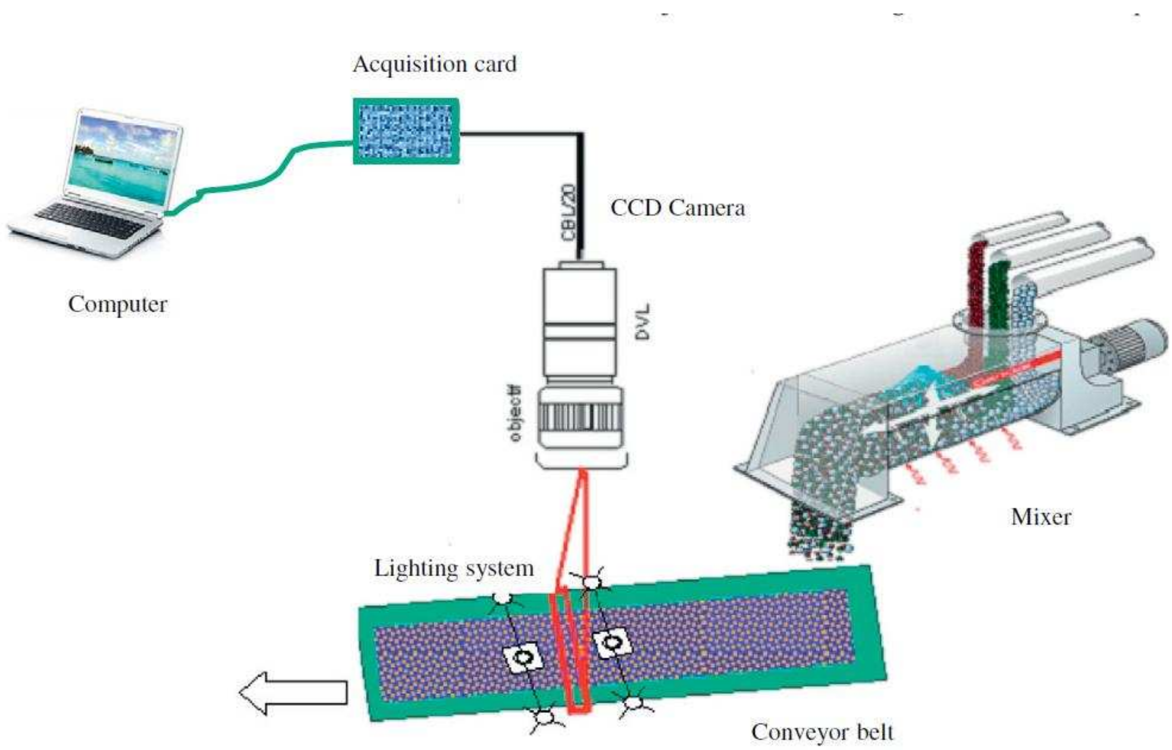


Fig. 4. The combined mixer/image-processing for on-line monitoring of continuous mixing, (Reprinted from G. Ammarcha et al. [51]).

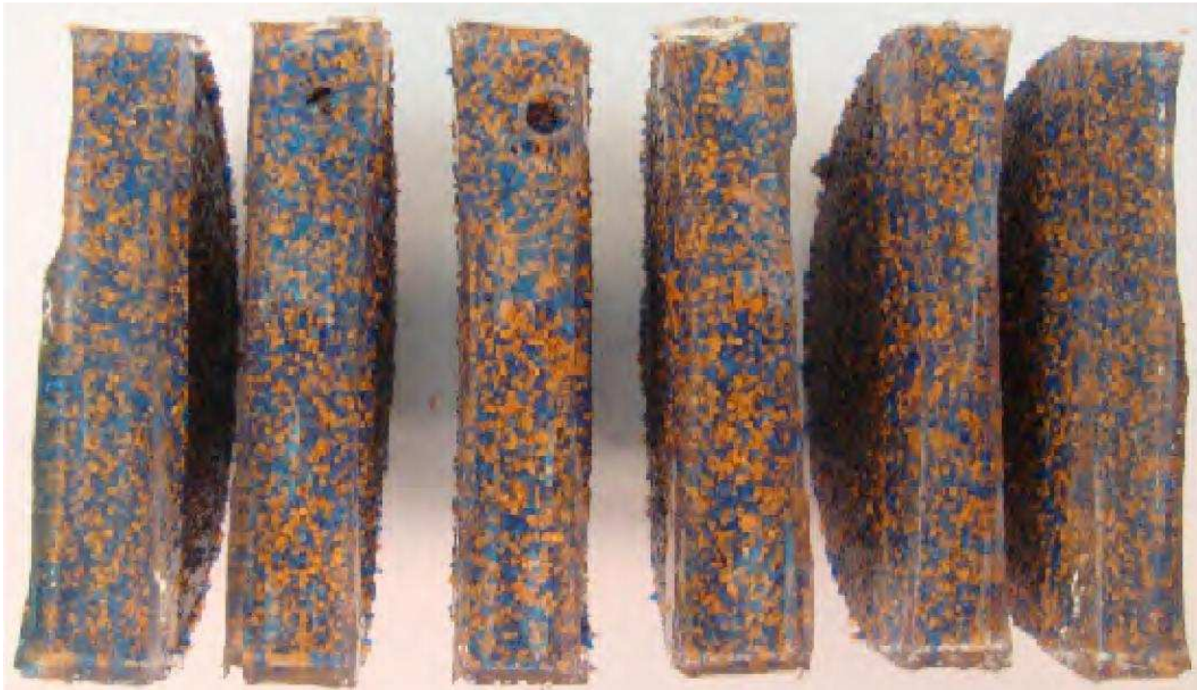
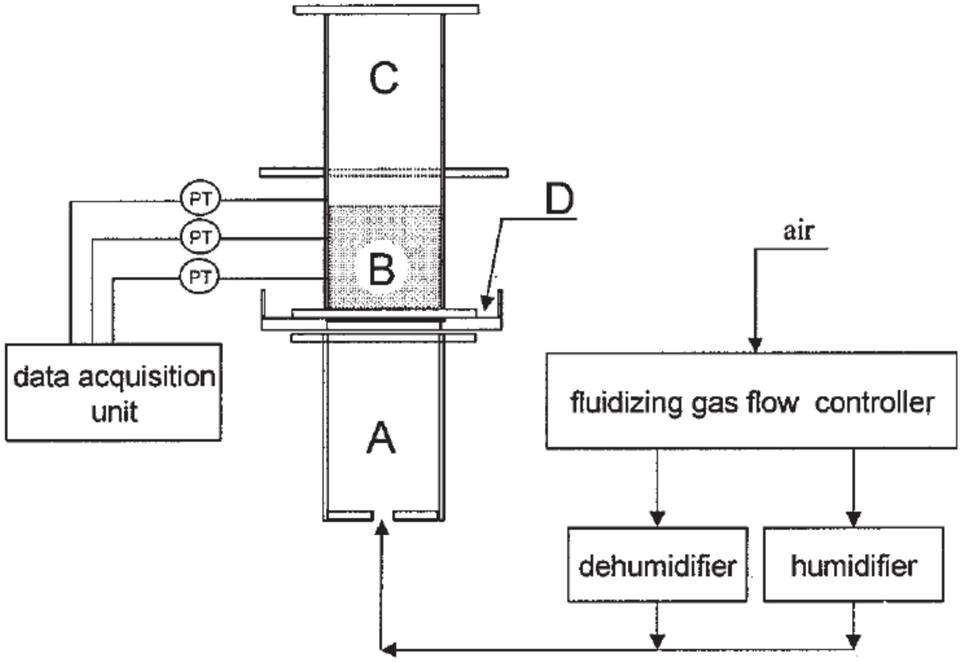
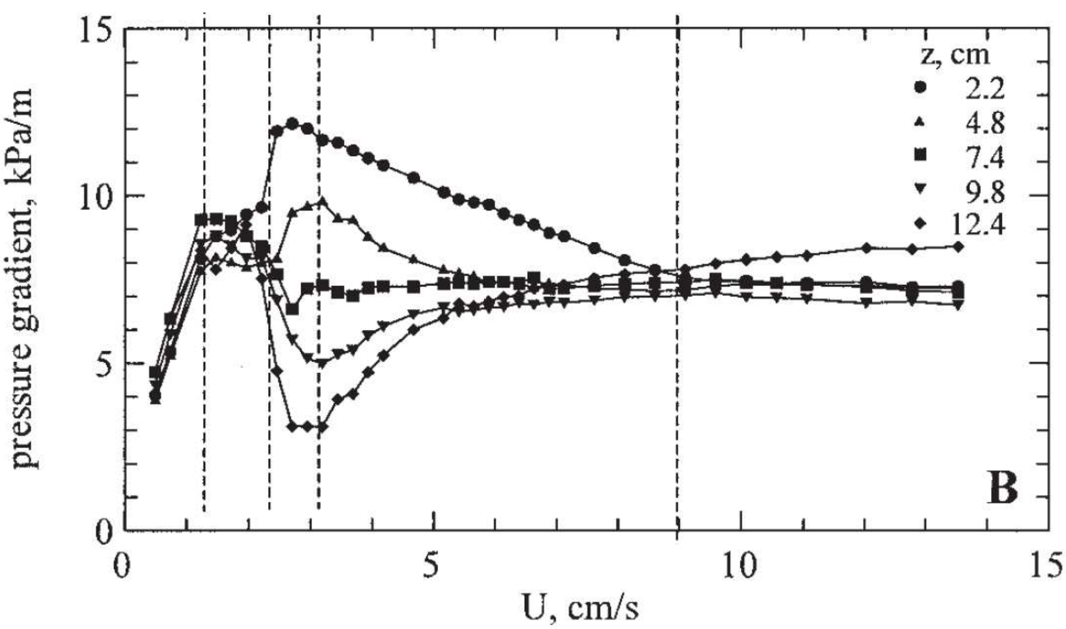


Fig. 5. The top view of the sliced samples after solidification of a homogenised mixture, (Reprinted from A. Realpe et al. [60]).

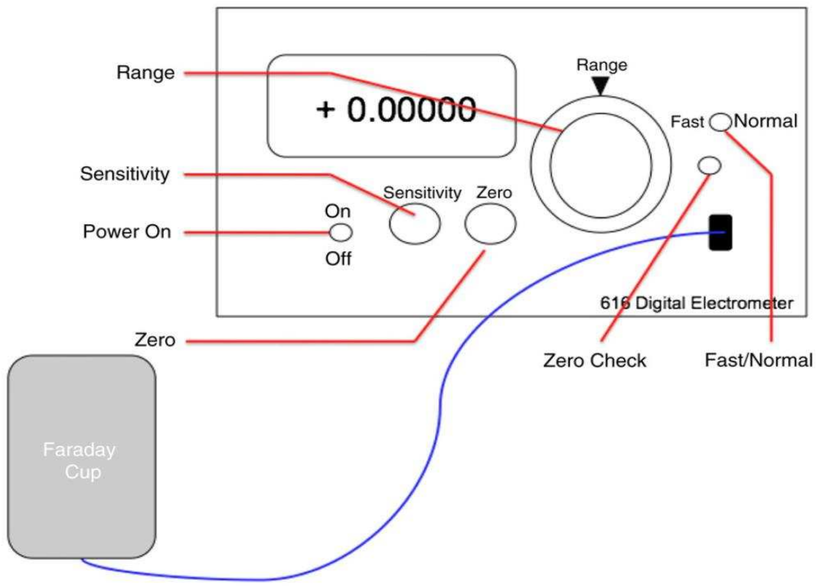


(a)

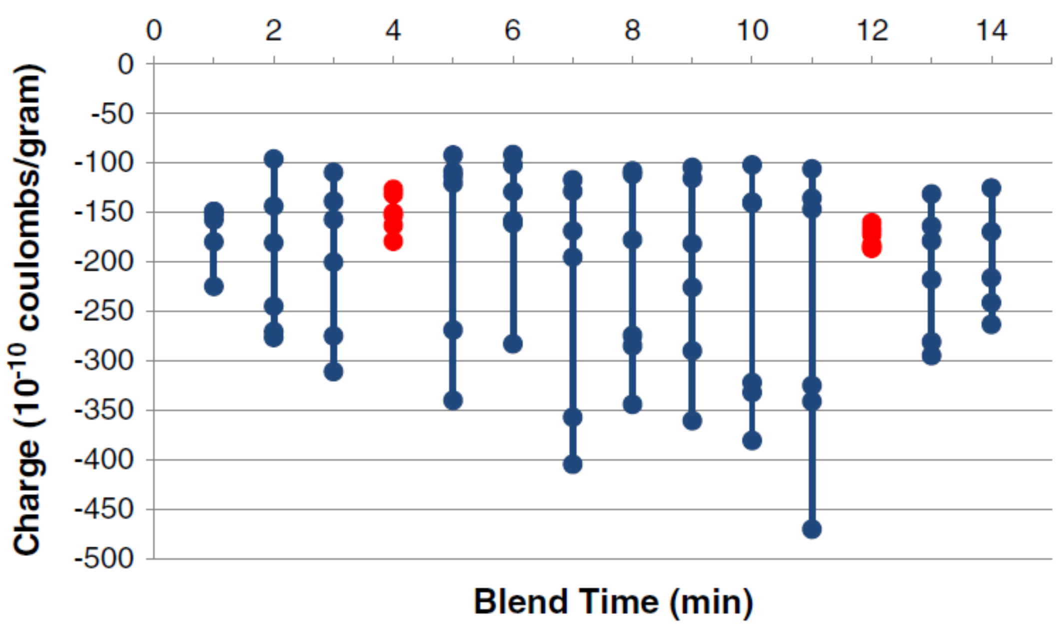


(b)

Fig. 6. (a) Schematic of fluidized bed equipped with pressure transducer (PT) and (b) pressure gradient versus gas superficial velocity at different heights of the bed, (Reprinted from Olivieri et al. [61]).

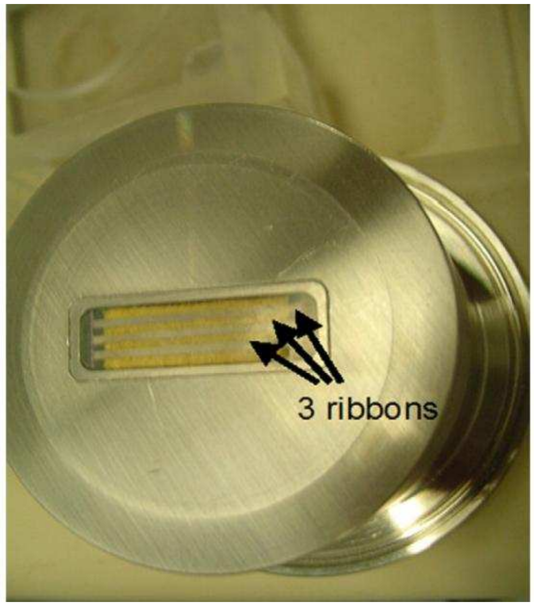


(a)

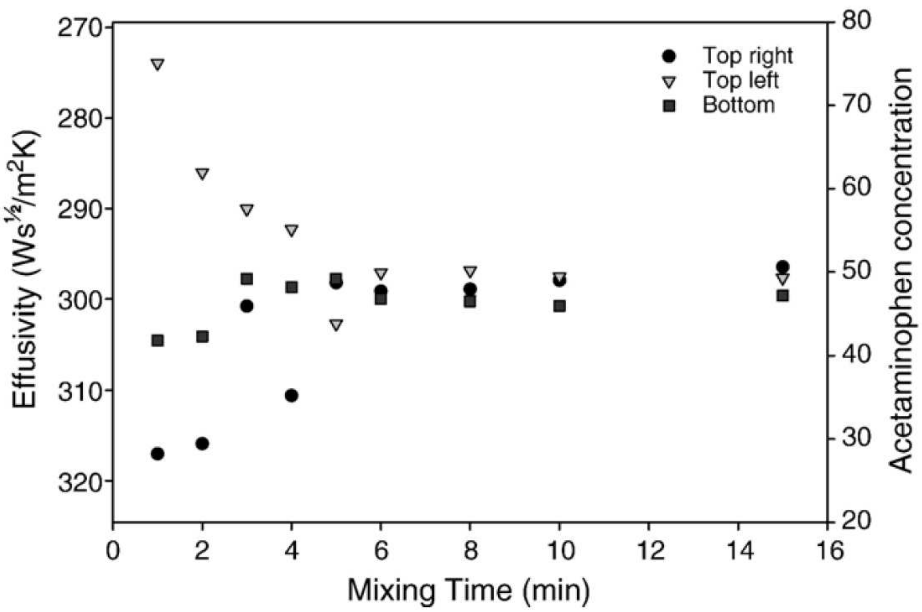


(b)

Fig. 7. (a) A simple schematic of Faraday Cup and (b) charge versus blend time plotted for Blend 1 (200 *g* batch, 98.75% Avicel PH200, 0.50% Cab-o-sil, 0.75% Magnesium Stearate, Reprinted from Hao et al. [65]).

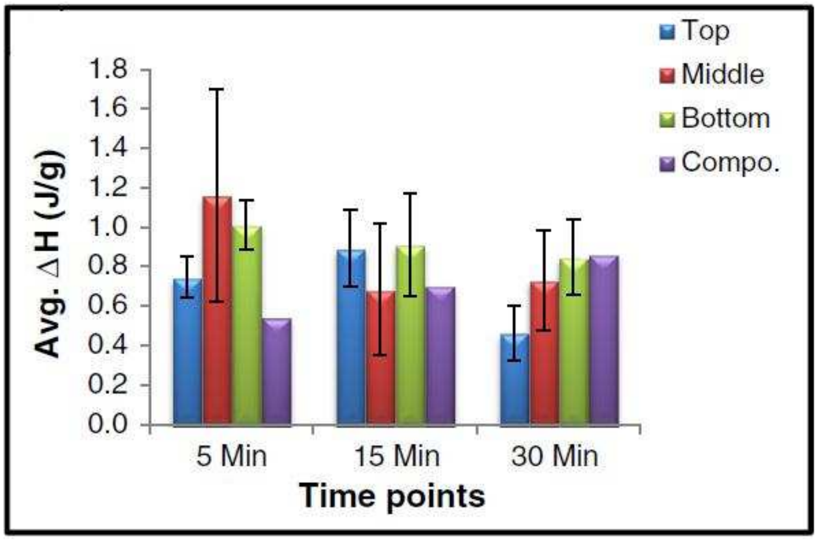


(a)

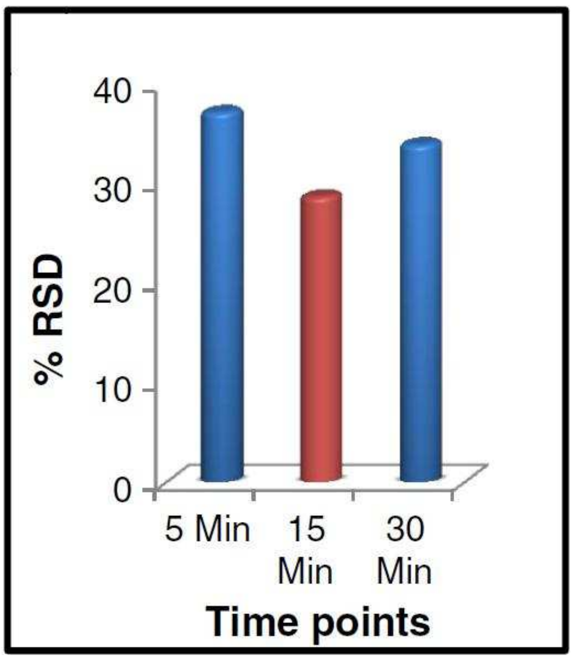


(b)

Fig. 8. (a) Schematic of BT-01™ unit and (b) evaluation of Acetaminophen homogeneity at three sampling positions of a V-blender using effusivity measurement, (Reprinted from Leonard et al. [68]).

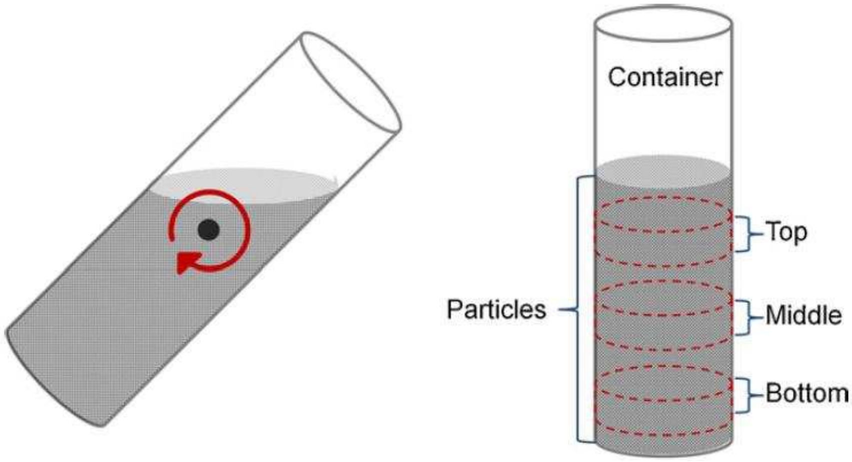


(a)

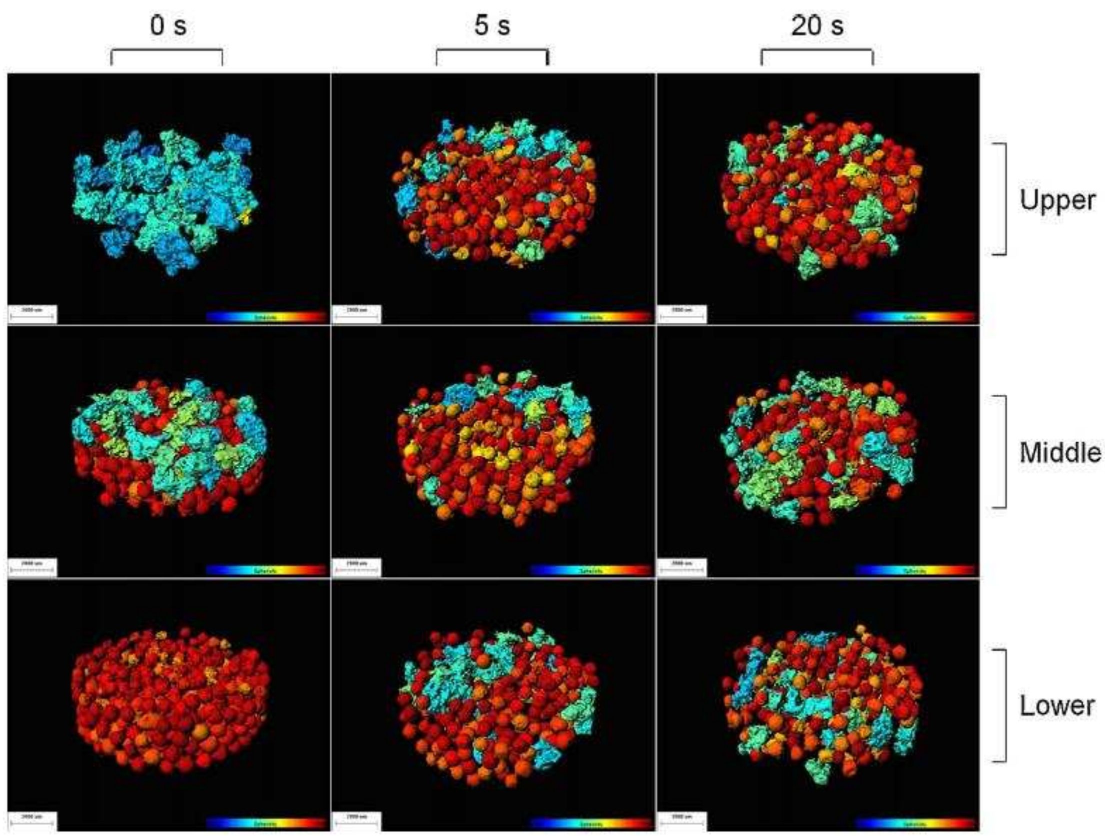


(b)

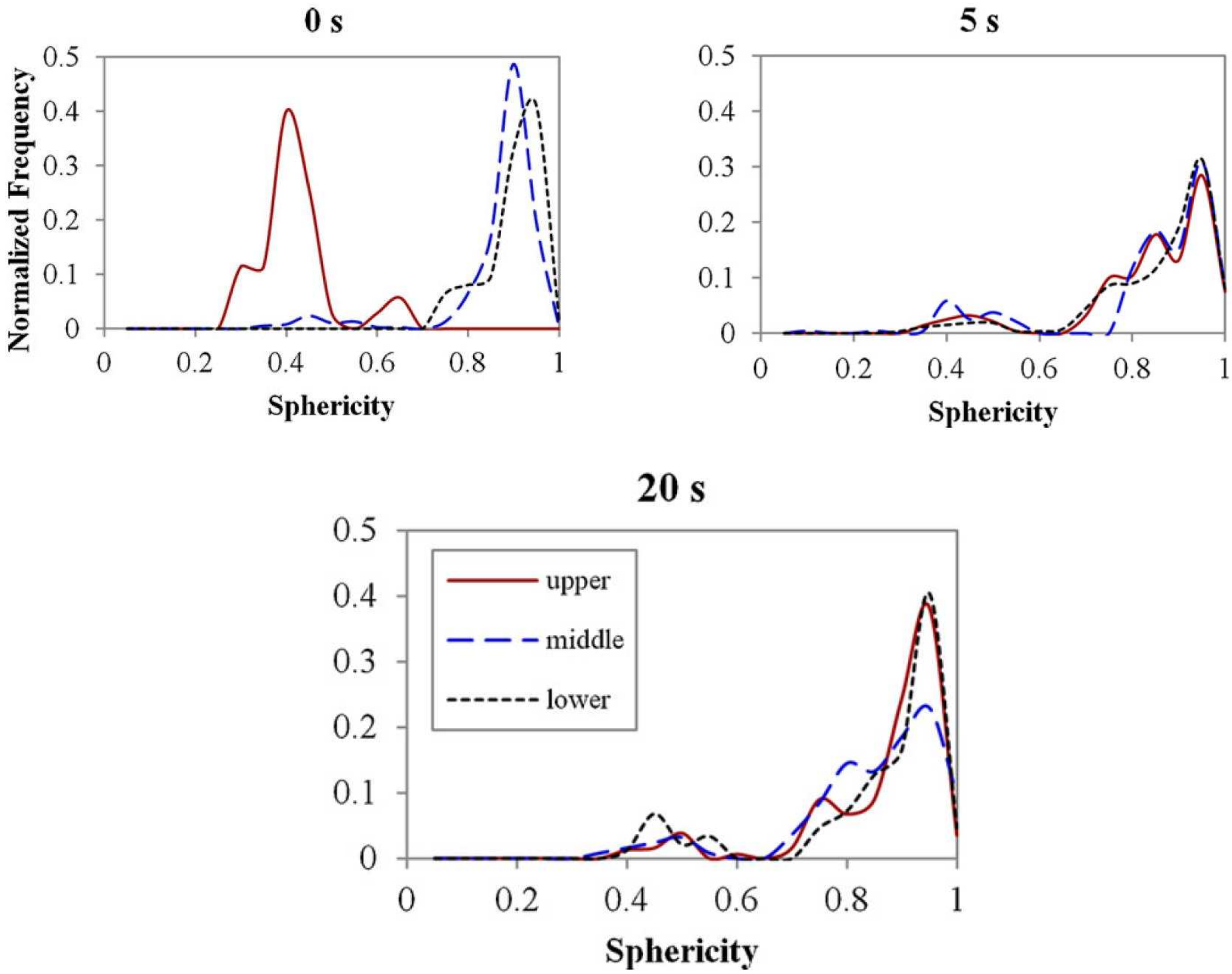
Fig. 9. (a) Average enthalpy changes of top, middle and bottom samples in the mixer and (b) % *RSD* of top, middle and bottom samples of microcrystalline cellulose-Atenolol blend at different time points, (Reprinted from Bharvada et al. [70]).


Container
Particles
Top
Middle
Bottom

(a)

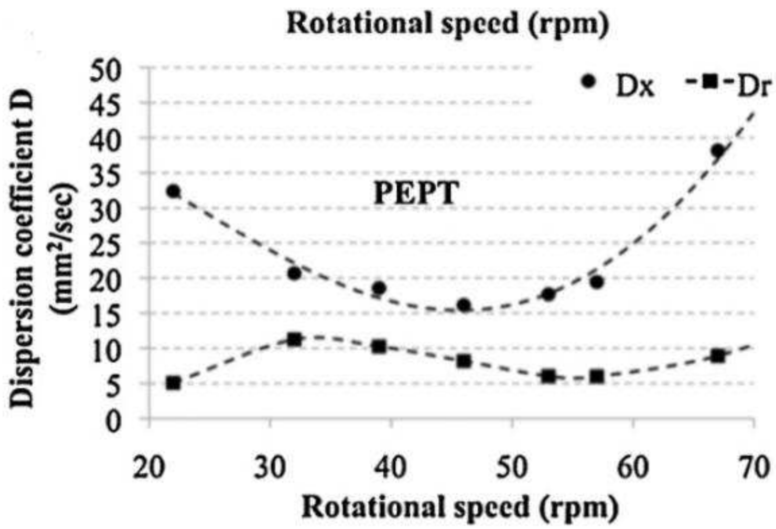

0 s
5 s
20 s
Upper
Middle
Lower

(b)

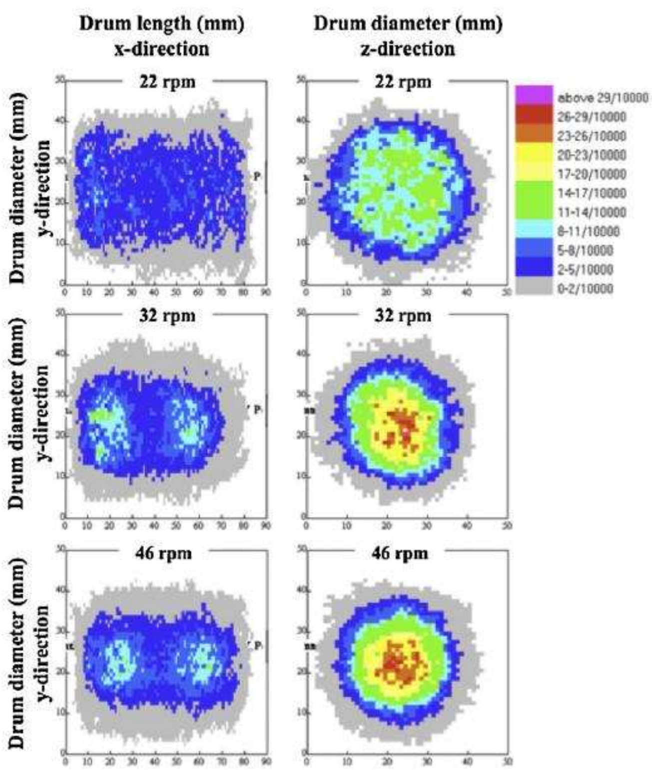


(c)

Fig. 10. (a) The schematic of mixing process, (b) images taken at different times of rotation and (c) evaluation of the mixing performance by normalized frequency distribution, (Reprinted from Liu et al. [73]).



(a)



(b)

Fig. 11. (a) Comparison of dispersion coefficients, D_x and D_r, as a function of rotation speed and (b) occupancy plots for 20 *min* measurement time, (Reprinted from Marigo et al. [81] with permission from Elsevier).

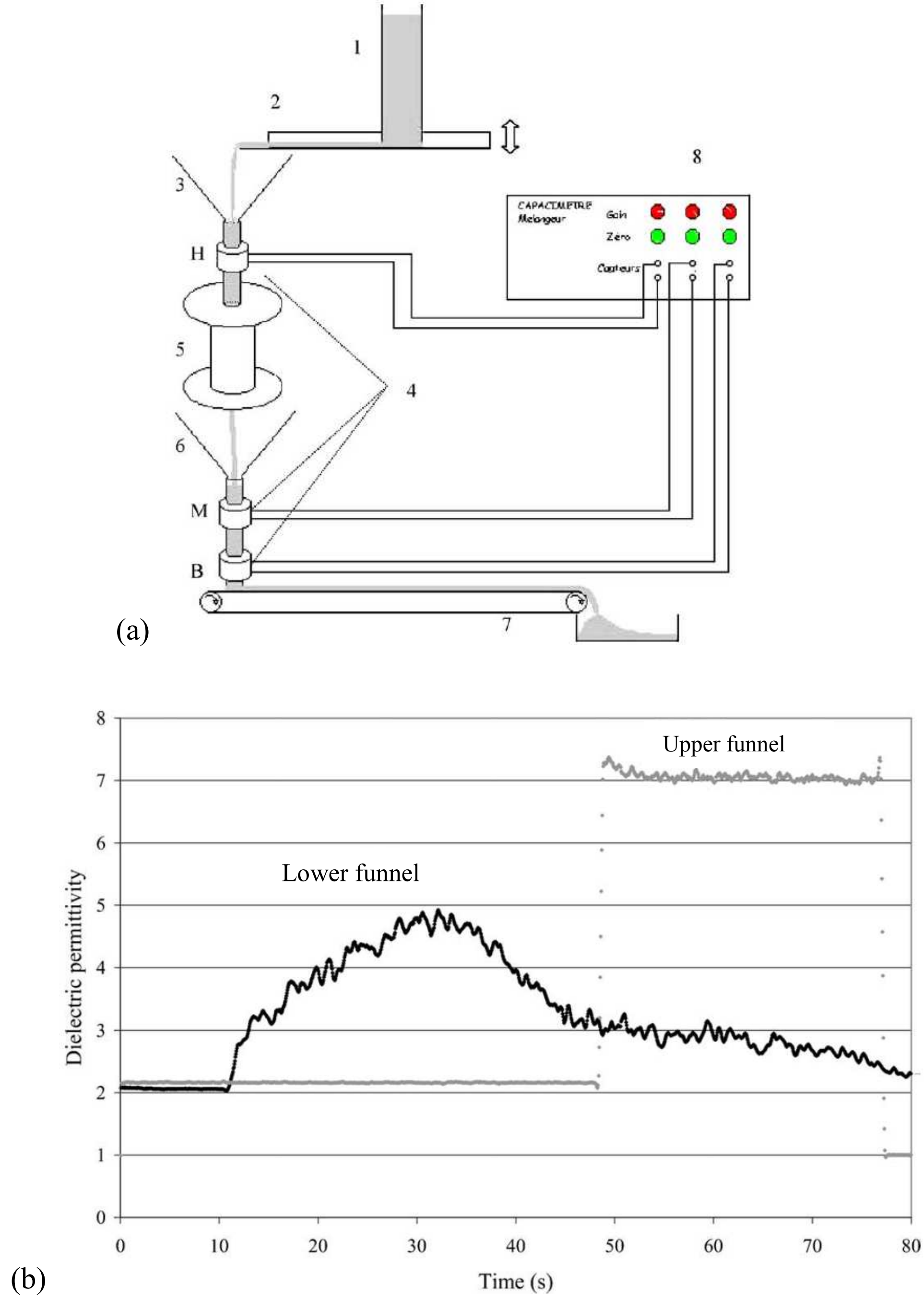
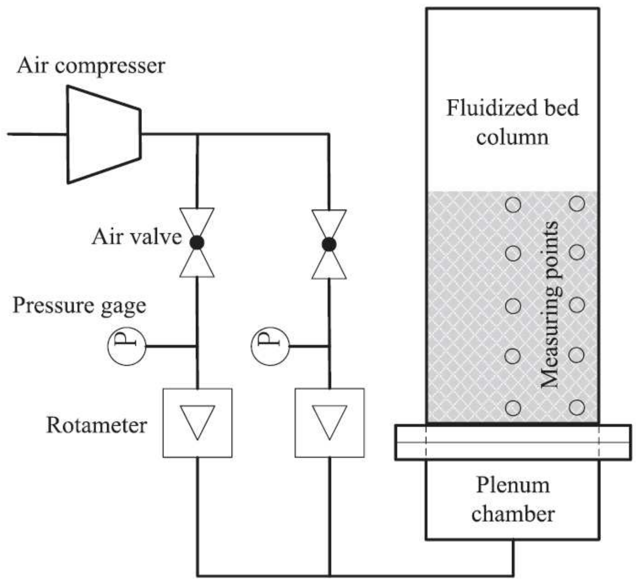
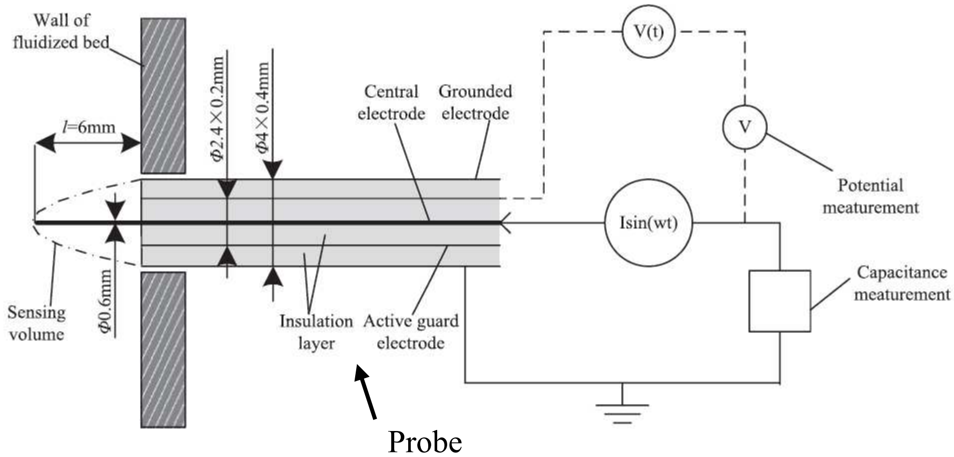
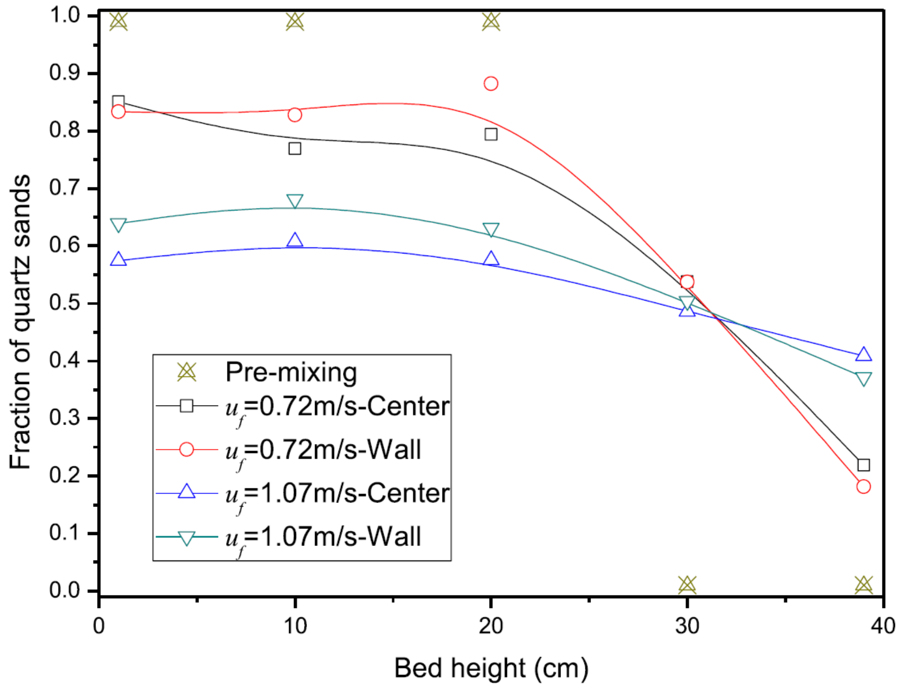


Fig. 12. (a) Schematic of the experimental rig comprising the intial mixture (1), vibrating channel (2), upper funnel (3), sensors (4), static mixer (5), lower funnel (6), belt conveyor (7) and capacimeter (8), (b) discharge profiles through a funnel, (Reprinted from Ehrhardt et al. [85]).


Air compresser
Fluidized bed column
Air valve
Pressure gage
P
P
Measuring points
Rotameter
Plenum chamber


Wall of fluidized bed
Φ2.4×0.2mm
Φ4×0.4mm
V(t)
Central electrode
Grounded electrode
l=6mm
V
Potential meaturement
Isin(wt)
Capacitance meaturement
Sensing volume
Φ0.6mm
Insulation layer
Active guard electrode
Probe

(a)



(b)

Fig. 13. (a) Schematic of fluidization experiment and the structure of capacitance probe and (b) fraction distribution of sand in polypropylene plastic and quartz sand mixture, (Reprinted from Huang et al. [86]).

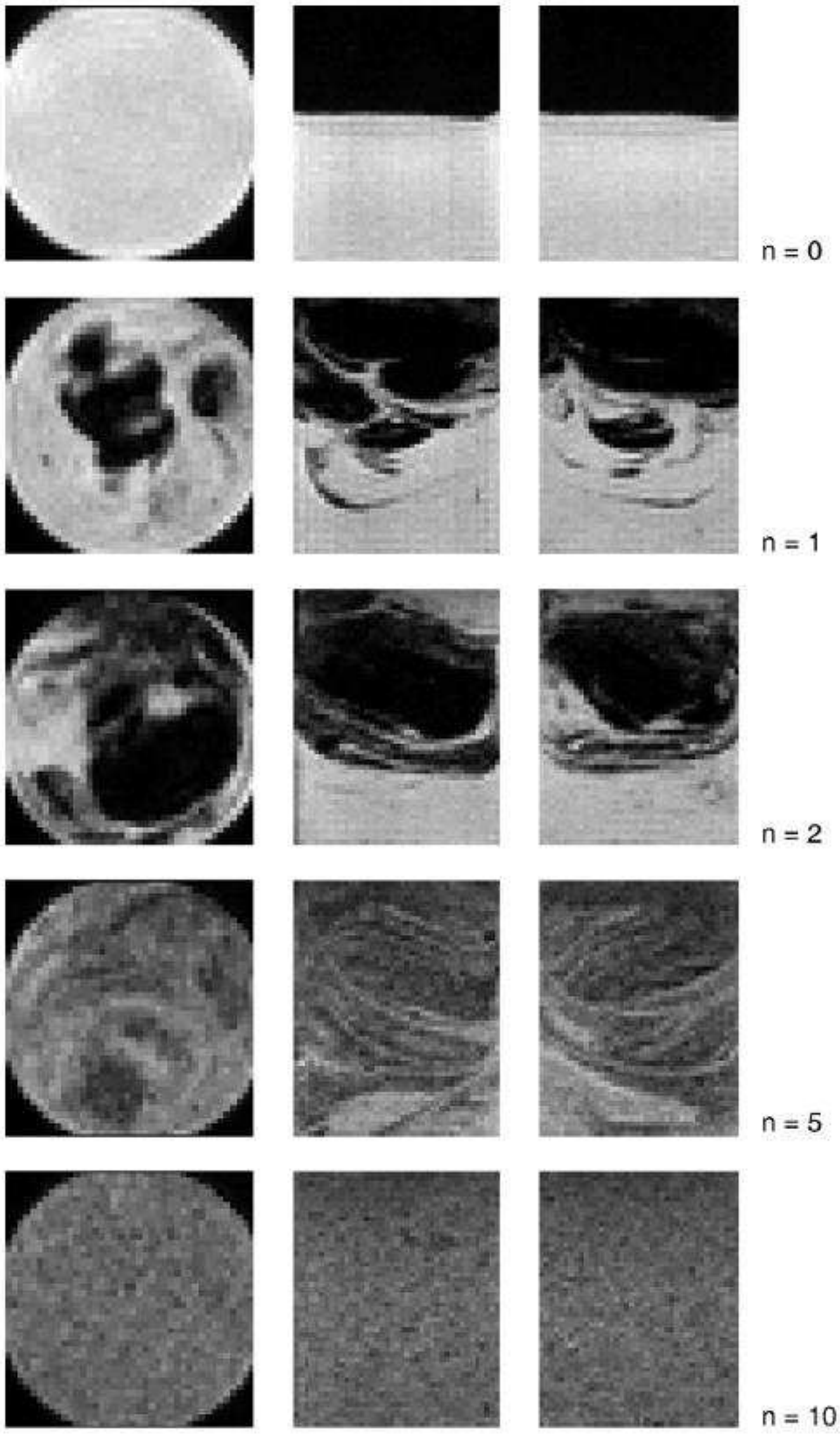
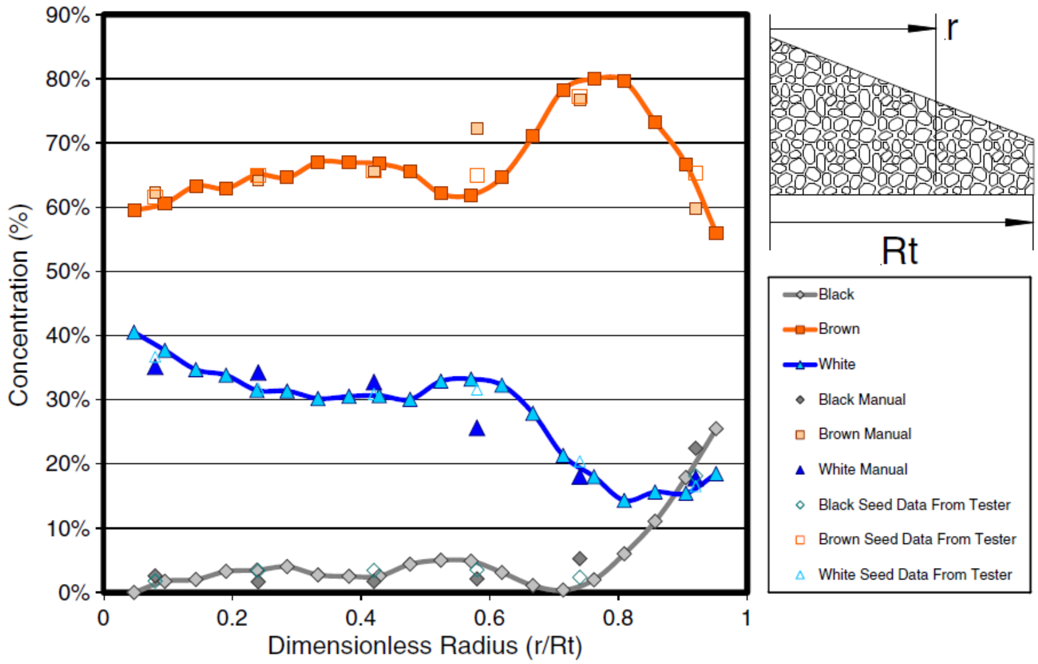
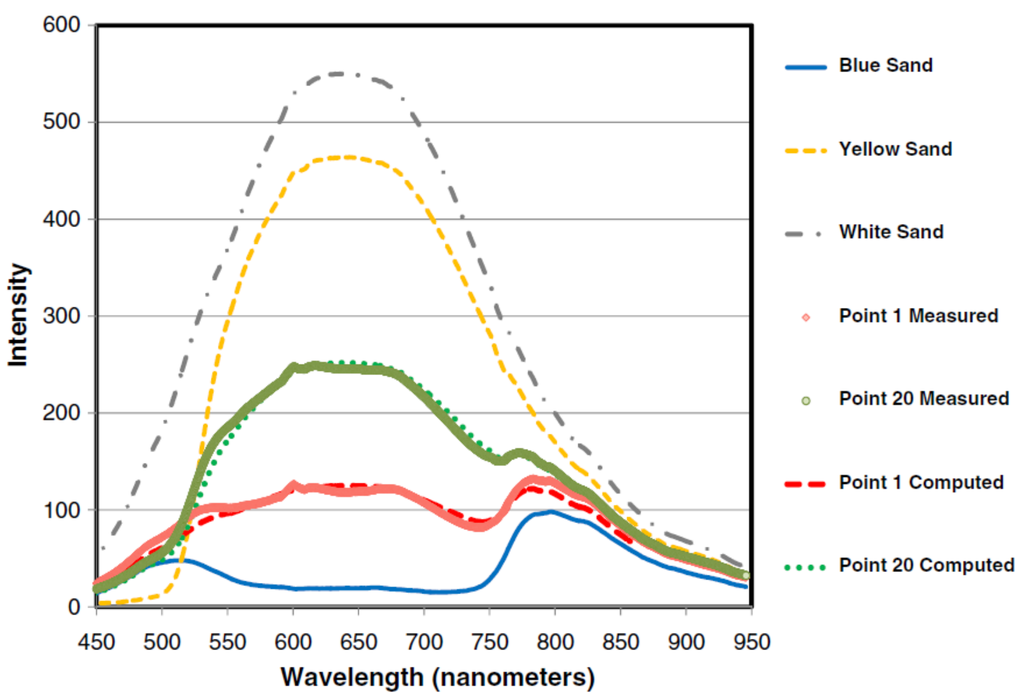


Fig. 14. MRI slices through a cylindrical powder sample at different time steps, (Reprinted from Hardy et al. [88]).



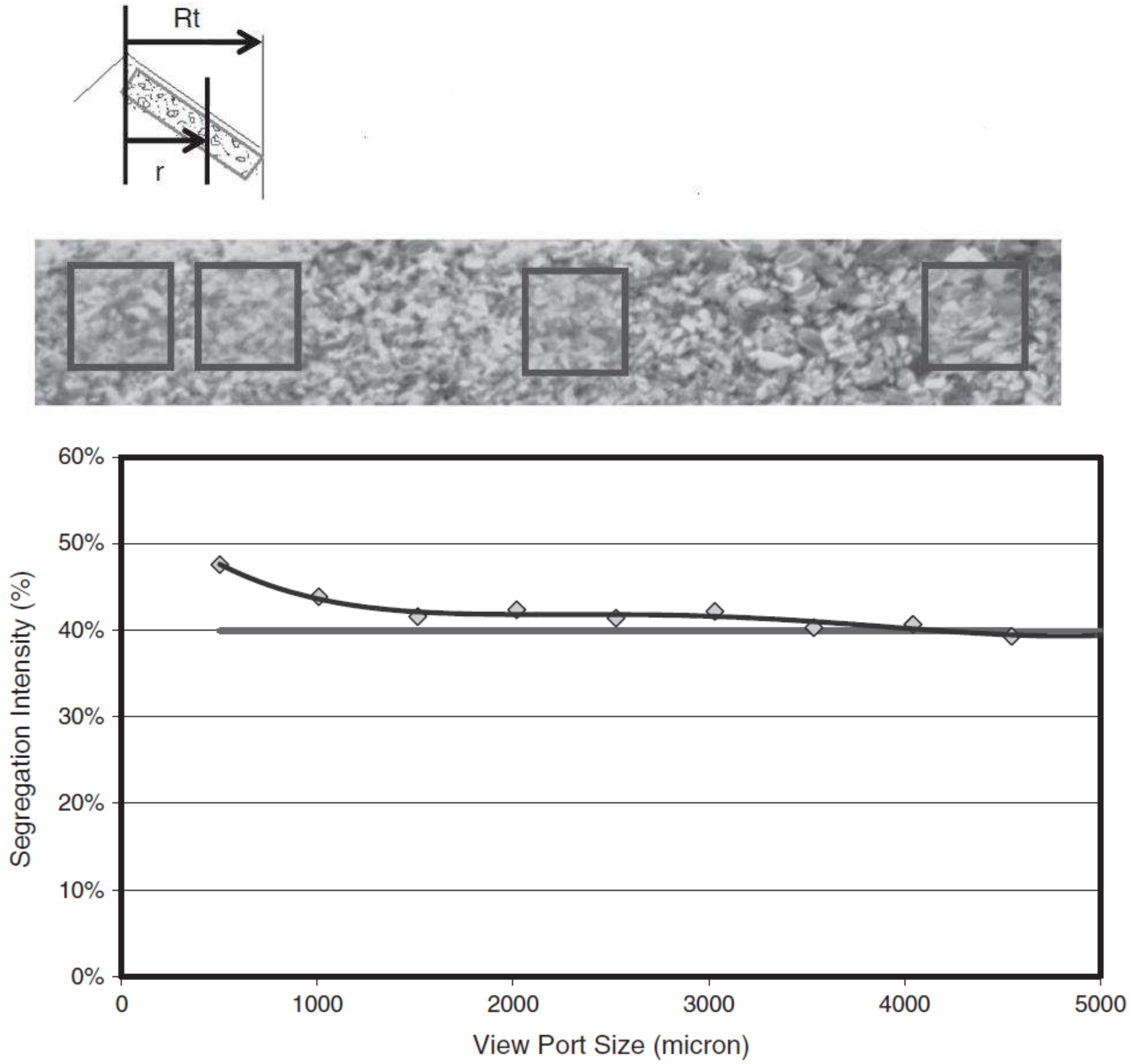
Concentration (%)
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
0
0.2
0.4
0.6
0.8
1
Dimensionless Radius (r/Rt)
r
Rt
Black
Brown
White
Black Manual
Brown Manual
White Manual
Black Seed Data From Tester
Brown Seed Data From Tester
White Seed Data From Tester

(a)



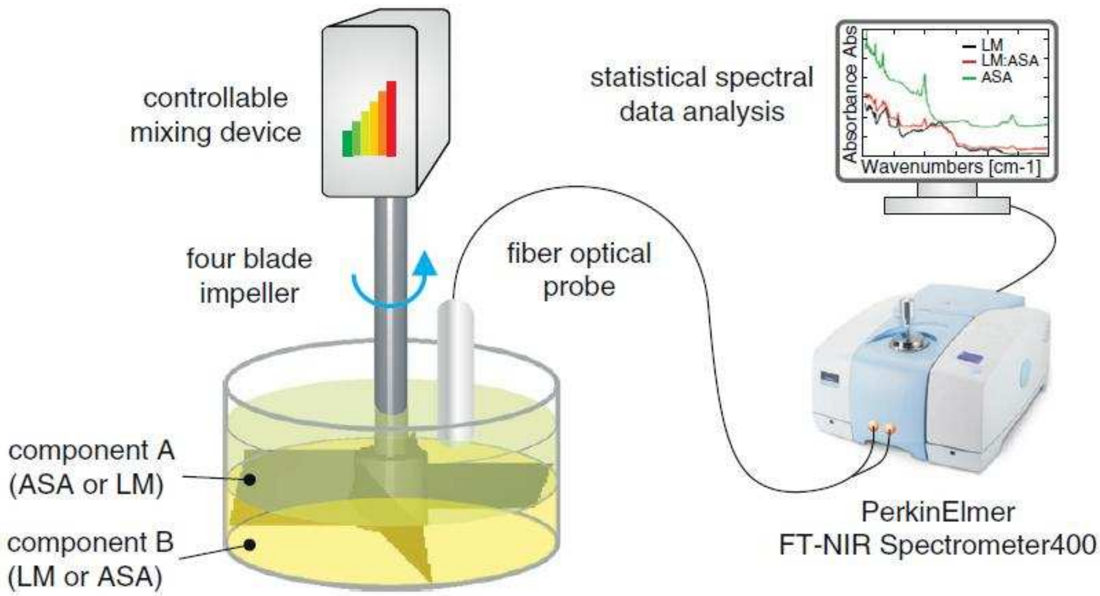
Intensity
600
500
400
300
200
100
0
450
500
550
600
650
700
750
800
850
900
950
Wavelength (nanometers)
Blue Sand
Yellow Sand
White Sand
Point 1 Measured
Point 20 Measured
Point 1 Computed
Point 20 Computed

(b)

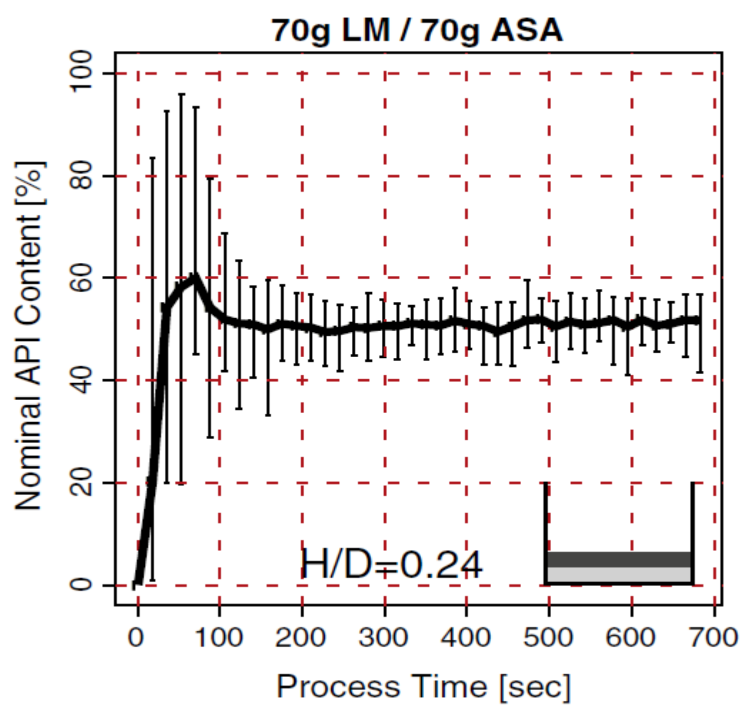


(c)

Fig. 15. (a) Concentration profiles of segregation for a mixture of three bird seeds and (b) spectra of pure components and mixture and (c) segregation intensity as a function of viewport size, (Reprinted from Johanson [116]).

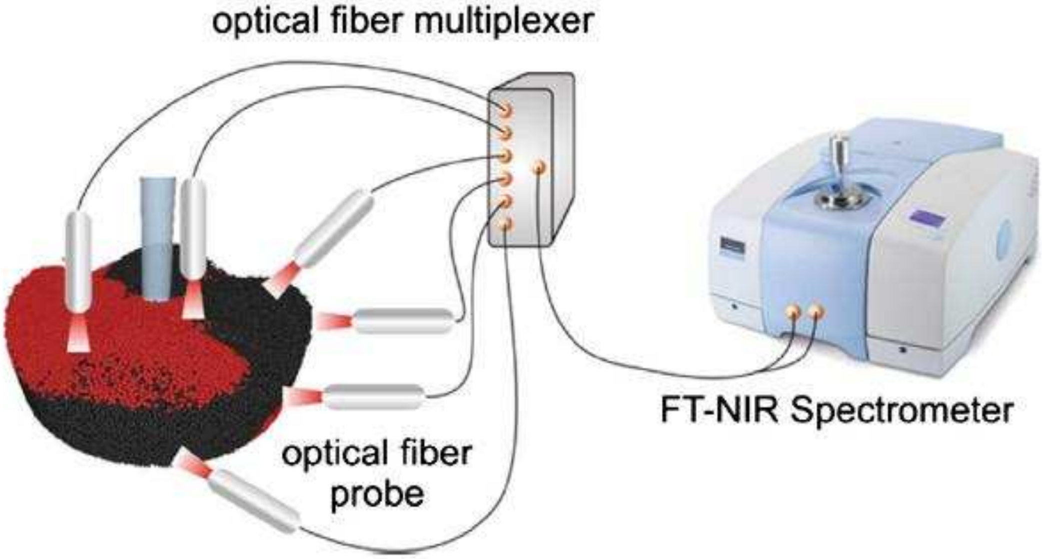


(a)



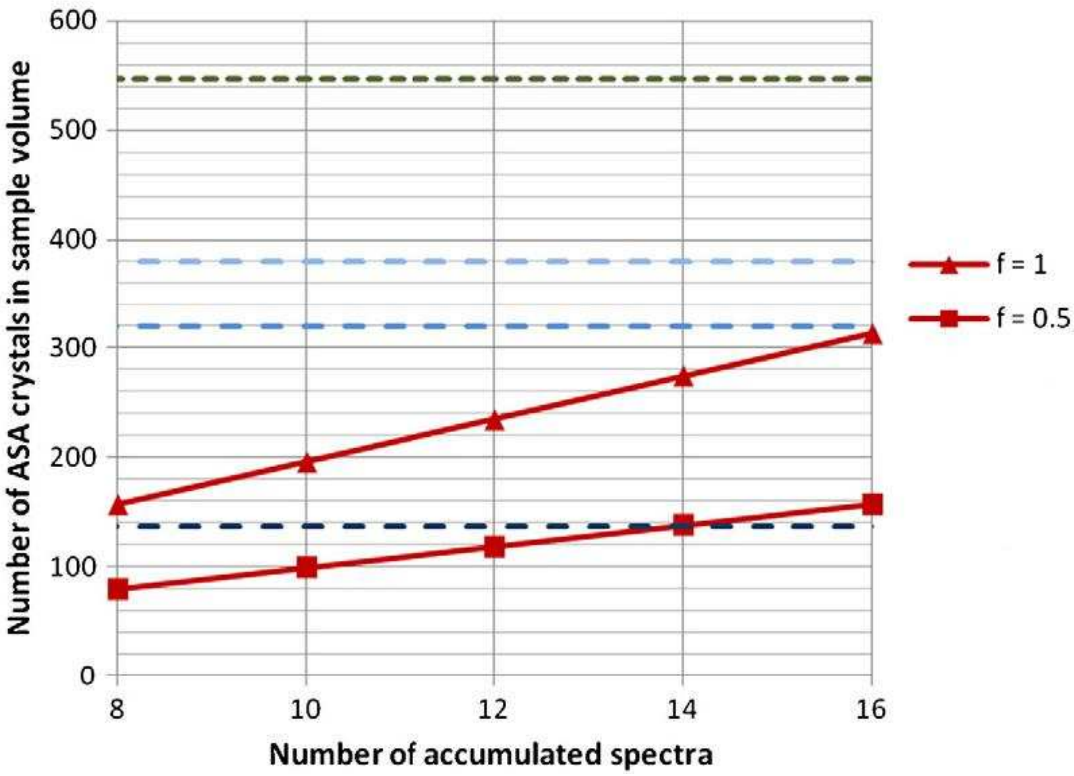
(b)

Fig. 16. (a) Experimental of an in-line NIR setup with a four-bladed mixer connected to a controllable mixing device and (b) blending plots for the mixer, light grey represents acetyl salicylic acid (ASA) and dark grey shows α-lactose Monohydrate, (Reprinted from Koller et al. [119]).



optical fiber multiplexer
FT-NIR Spectrometer
optical fiber
probe

(a)



Number of ASA crystals in sample volume
Number of accumulated spectra
f = 1
f = 0.5
0
100
200
300
400
500
600
8
10
12
14
16

(b)

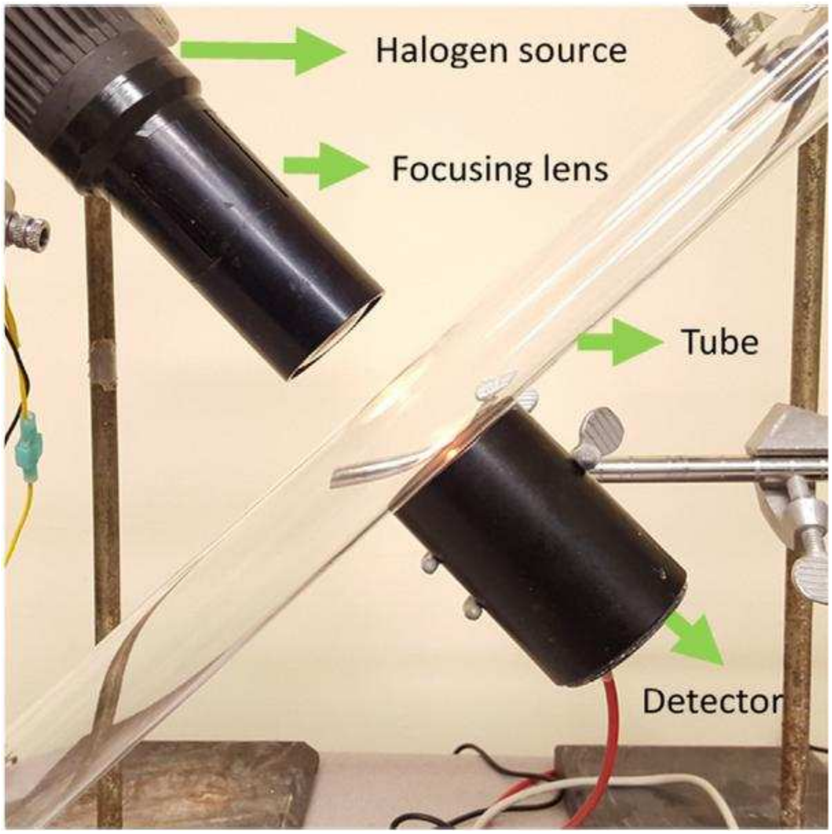
(c) 

Fig. 17. (a) Schematic of multi-probe spectroscopy setup, (b) dependence of the sample volume size to the number of accumulated spectra and the moving speed in front of the sensor window (f = 1 is the tip speed of the blade, f = 0.5 is half of this speed) and (c) continuous blend monitoring of powder streams using transmission NIR, (Reprinted from Scheibelhofer et al. [121] and Reprinted from Alam et al. [122]).

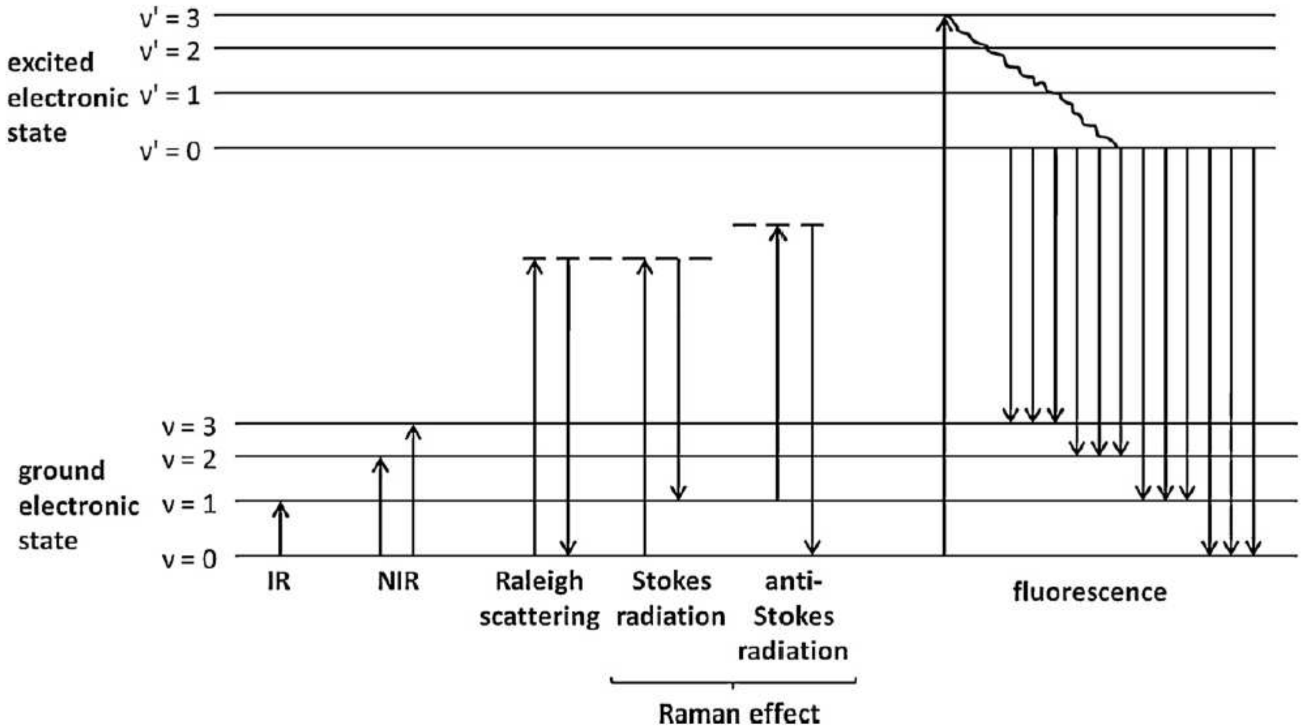


Fig. 18. IR and NIR absorption, the Raman effect and fluorescence, (Reprinted from De Beer et al. [25]).

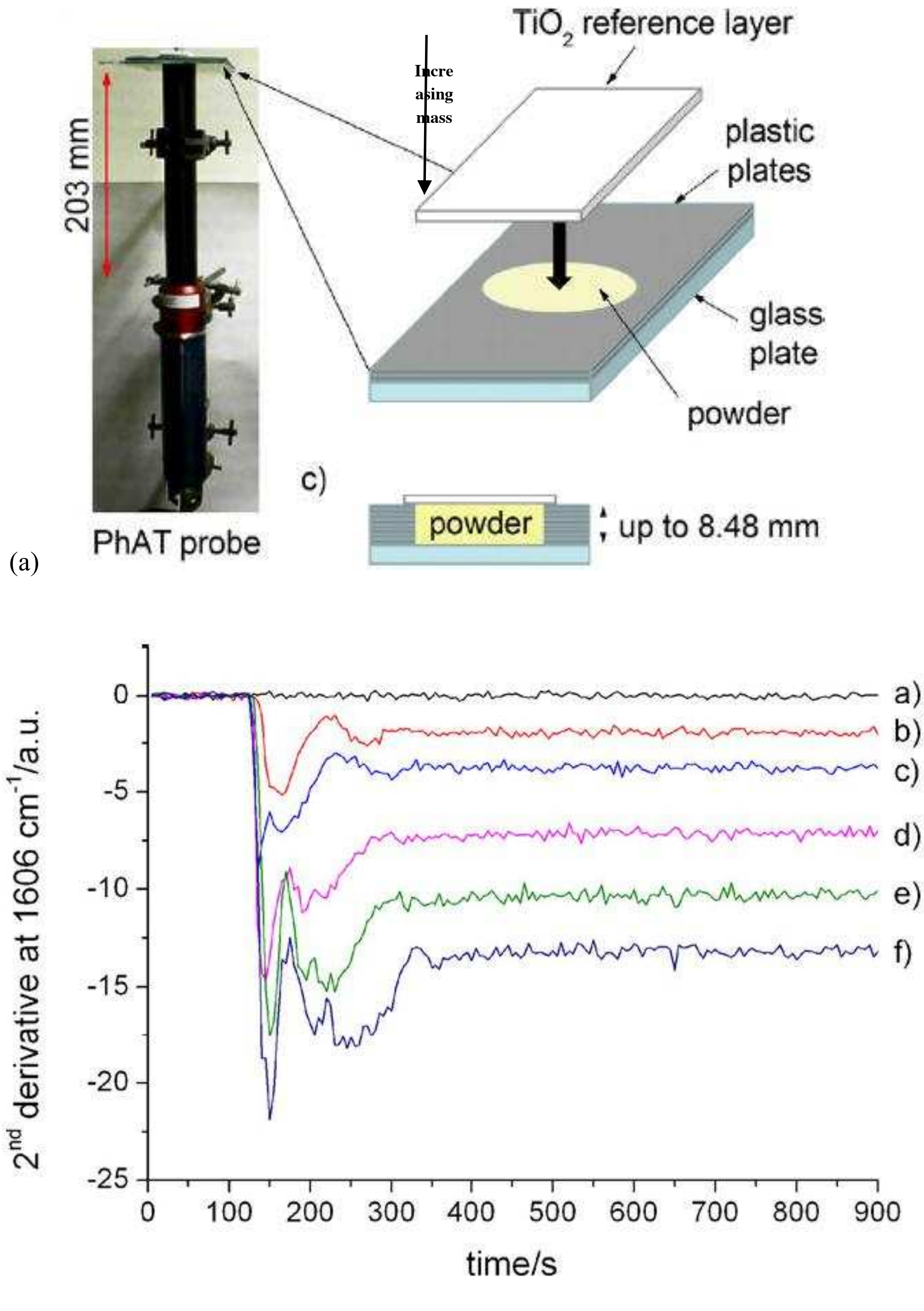
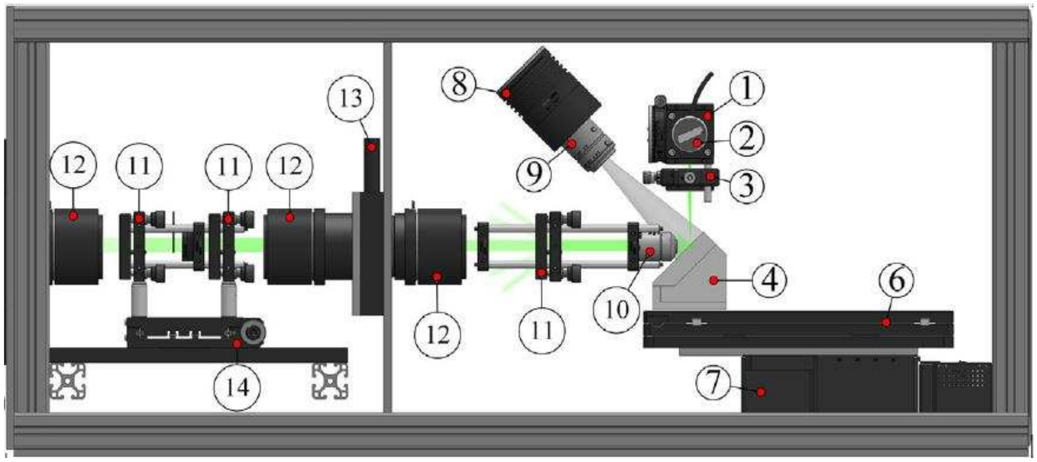
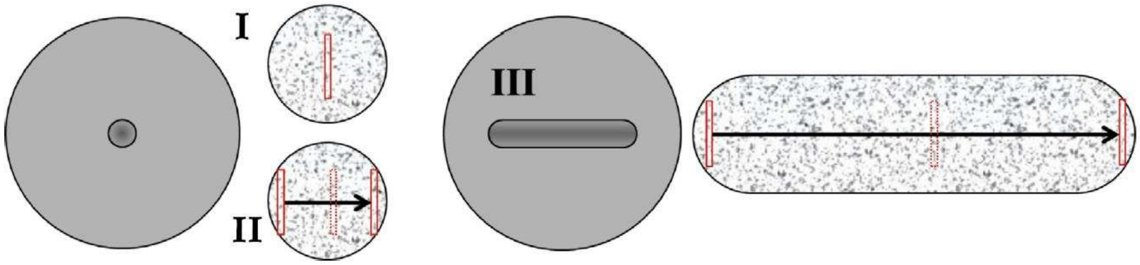


Fig. 19. (a) Schematic of Raman PhAT probe and sample set up and (b) Raman PhAT probe mixing profiles at 1606 cm^{-1} for the case of the addition of different amounts of aspirin to Avicel, (Reprinted from Allan et al. [125]).

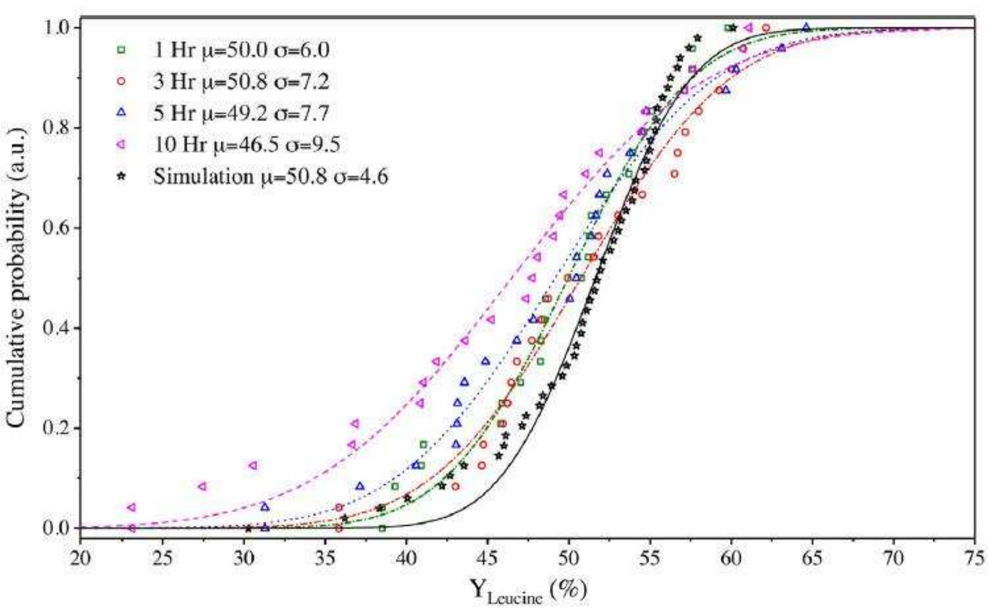


(a)

(1) UV fused silica broadband plate splitter, (2) power meter, (3) plano-convex lens, (4) aluminum block, (5) square pin stub holder, (6, 7) motorized X-Y-Z stage, (8) illuminating lamp, (9) monitoring camera, (10) microscope, (11) narrow-band notch filters, (12) Nikon lenses, (13) manual slit, (14) filters.

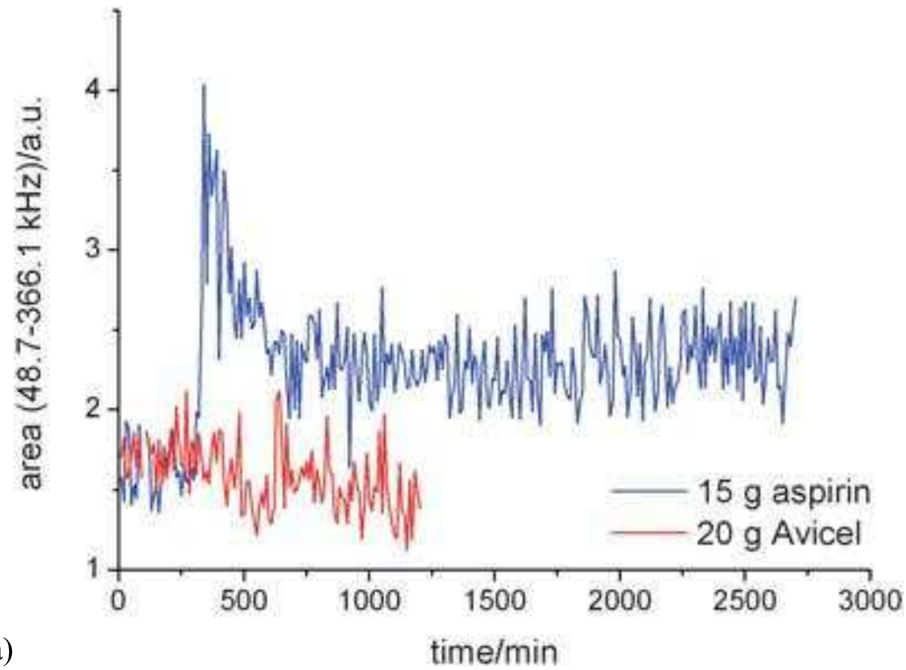


(b)

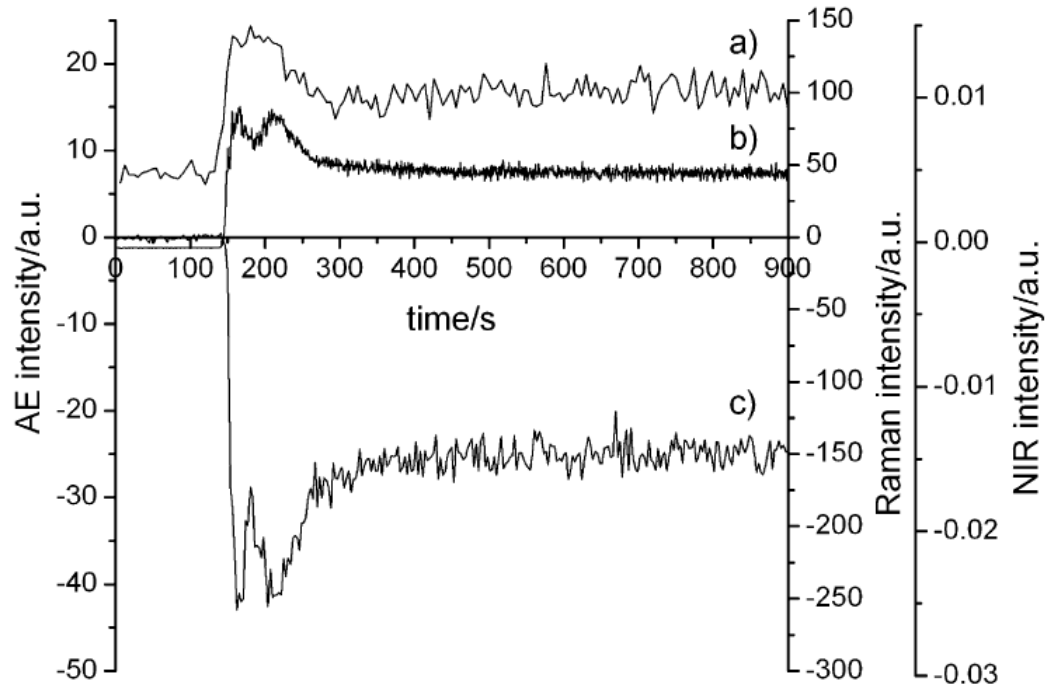


(c)

Fig. 20. (a) Dispersive macro-Raman Set-up, (b) different sampling methods: single spot (I), scanning across the cavity (II), scanning along the groove (III) and (c) cumulative distributions of the measured leucine mass fraction during mechanical mixing, (Reprinted from Wang et al. [126]).

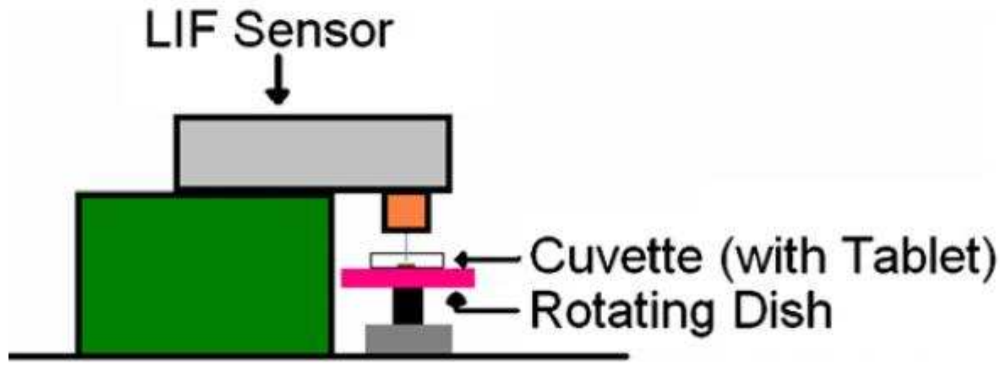


(a)

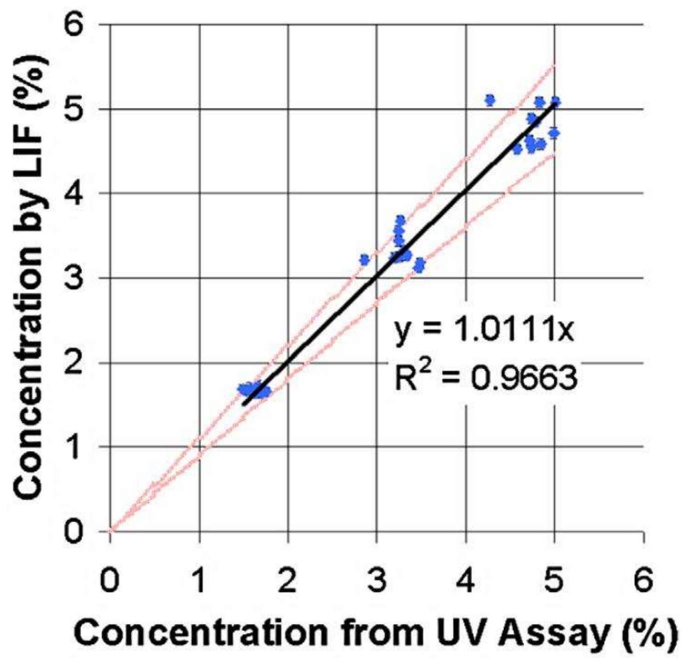


(b)

Fig. 21. (a) Acoustic emission mixing profiles and (b) mixing profiles for the addition of 30 *g* aspirin to 75 *g* Avicel, (Reprinted from Allan et al. [125, 132]).



(a)



(b)

Fig. 22. (a) LIF instrument and (b) triamterene concentration obtained using LIF and UV analysis, (Reprinted from Domike et al. [135]).

Table

Table 1. Research works based on image analysis for powder blend uniformity evaluation.

Objectives	Instrument for the image analysis	Reference
Investigation of a double cone system for the mixing of glass beads of different colours: Mixing performance has been done by computing the concentration of each species in each discretized square MATLAB software was used to determine the number of particles in discretized images	Camcorder at the rate of 40 frames per second	[52]
-Investigation of the component distribution of counterfeit Viagra and Cialis tablets using image processing: Bhattacharyya distance was performed as a measure of mixture quality	Video Spectral Comparator (A high resolution VSC 5000)	[53]
-Evaluation of the segregation in pseudo-2D beds using a state-of-the-art digital colour camera: Sample colour variance was performed as a measure of mixture quality	A digital image analysis technique (AT-200 GE)	[54]
-Investigation of the component distribution of dropping glass beads with two different sizes using image analysis method: Image obtained by the camera was converted to an indexed image using MATLAB software Two indices ($I_\perp$ and I_H) were used to distinguish	Nikon D70 digital camera	[55]

between the segregation and stratification mechanisms.		
-Segregation analysis of horizontally shaken monolayers of different binary mixtures on a vibrating tray: The position of individual components was estimated using image processing, developed in MATLAB software	CCD Nikon camera	[56]
-Evaluation of the mixing time of coloured particles in a rotary drum: RGB colour analysis was provided using image Processing Toolbox provided by MATLAB software Degree of particle mixing was described using variance method	Video camera at a frame rate of 25 fps	[57]
-Evaluation of the effect of paddle rotational speed on the mixing performance of the agitation process in a electrophotographic system: The beads velocity field during agitation was used to describe the mixing extent	High speed camera (MotionPro HS-4)	[58]
- Investigation of the mechanism of dead zone formation: The effect of different mixing parameters (size, packing of particles, speed and shape of the mixer)	Canon EOS 600D camera	[59]

on the degree of mixing was evaluated.		

Table 2. Summary of different tomographic techniques for powder mixing assessment.

No.	Objective	Materials	Technique	Reference
1	Mixing investigation of binary mixtures of free flowing particles in a Turbula® mixer	Sugar beads	MRI	[93]
2	Characterization of the kinematics of mixing/size segregation of dried binary mixtures	Poppy seeds and sugar beads	MRI	[94]
3	Investigation of the solid concentration changes during granular flow in a cylindrical model silo	Different type of sands	ECT	[95]
4	Evaluation of the size segregation in a cold fluidized bed at atmospheric pressure	Spherical glass particles	ECT	[96]
5	Evaluation of the mixing and segregation in a fluidized bed	Ground walnut shell particles and glass beads	µCT	[97]
6	Assessment of the mixing in an industrially static	Glycerol	Combined PEPT and	[98]

	mixer geometry		MRI	
7	Estimation of the spatial distribution of components throughout the tablets	Potassium chloride, spray-dried lactose	µCT	[99]
8	Investigation of the axial mixing and segregation of fuel at different operational conditions of bubbling fluidized bed	Tracer particles with solid density representing biomass char	Magnetic particle tracking (MPT)	[100]

Table 3. Current researches investigating the powder blend uniformity using NIR system.

No.	**Objective**	**Instrument**	**Blending materials**	**Reference**
1	End-point determination of a pharmaceutical blending	Sentronic GmbH NIR spectrometer	API (Active Pharmaceutical Ingredient), crospovidone, lactose, and microcrystalline cellulose	[103]
2	Application of Near Infrared hyperspectral imaging for the evaluation of the spatial distribution of drugs in tablets	OPOTEK Inc. NIR system	Tolmetin sodium dehydrate, anhydrous lactose, magnesium stearate	[104]
	Evaluation of the effects	FT-NIR spectrometer	Aspirin, lactose,	[105]

3	of granule cohesion and size on the in-homogeneity tendency of pharmaceutical powders using NIR spectroscopy, bench scale sifting and fluidization segregation testers		microcrystalline cellulose, magnesium stearate	
4	Application of an in-line NIR spectroscopic method for the measurement of drug content of tablets during a continuous tableting process	Visio NIR	Acetaminophen, lactose and magnesium stearate	[106]
5	Implementation of a multi-point fiber optic based on NIR set-up to control the drug concentration at the discharge of a continuous mixer, comparison between in-line and off-line measurements	Multipoint NIR system	Acetaminophen, magnesium stearate and Avicel PH-200	[107]
6	Investigation of an in-line NIR spectroscopy for content uniformity analysis in an industrial tablet press	NIR spectrometer	API, EX1 (excipient1) and EX2	[108]

7	Non-contact monitoring of the blending process in pharmaceutical powder blends	NIR spectrometer	APAP, Avicel, Lactose	[109]
8	Evaluation of powder blend uniformity of a cohesive model formulation using a real-time NIR spectroscopy and an at-line NIR chemical imaging approach	Integrated Corona NIR spectrometer from Zeiss	Naproxen (API), microcrystalline cellulose , croscarmellose and free-flowing mannitol	[110]
9	Rapid determination of four structurally similar active pharmaceutical ingredients using a developed at-line Near Infrared method	A Bruker multi-purpose FT-NIR analyzer	Four APIs, microcrystalline cellulose as excipient	[111]
10	Investigation of the mixing performance of a laboratory-scale Resonant Acoustic® Mixer (LabRAM). The effect of process parameters (fill level, acceleration, and blending time) was considered	Transform Near-Infrared (FT-NIR) spectrometer	Micronized acetaminophen, granulated acetaminophen and caffeine	[112]

11	Evaluation of the blend mixing in a continuous/dynamic drug product manufacturing process	Fourier transform spectrometer	Acetaminophen, microcrystallinecellulose, mannitol, croscarmel-lose sodium, magnesium stearate	[113]
12	Investigation of NIR spectroscopy for overall quantitative analysis of all ingredients of laundry detergents	Bruker Multi Purpose Analizer	Washing powder ingredients	[114]
13	Evaluation of NIR spectroscopy technique for the quality control of semi-solid pharmaceutical formulations	NIR spectrometer	Nonionic hydrophilic cream, Salicylic acid and Erythromycin	[115]

Table 4. Powder uniformity assessment techniques with their advantages and disadvantages.

Method	**Advantage**	**Disadvantage**
UV-visible absorbance spectrophotometry	Simple to implement: Spectrophotometers are fairly straightforward instruments with very few moving parts - Fast analysis -Low cost maintenance	-Material is not recoverable using this method as it is dissolved in a solution (wet technique) -The sensitivity of a spectrophotometer is often inadequate at low concentrations

		-Absorption results can be influenced by other parameters, e.g. impurities, temperature and pH, leading to inaccurate results -Not a green method, as it produces liquid waste -Separate measurement of multi component fractions is not applicable -Error due to off-line sampling and disturbance of the powder bed (invasive)
High-Performance Liquid Chromatography	Accurate and sensitive for multi component quantification	-Costly and time consuming -Material is not recoverable using this method as it is dissolved in a solution (wet technique) -Not a green method, as it produces liquid waste -Error due to off-line sampling and disturbance of the powder bed (invasive)
Image analysis	- Simple to use	-No information on 3D

	-Green method (dry technique) - Low cost -Possible for blend uniformity assessment of multicomponent mixtures (providing that particles differ in colour) -Sample analysis can be performed non-intrusively	structure of powder mixtures (this method is surface sensitive). Nevertheless, if coupled with the slicing technique, the internal structural analysis of mixture could be provided -Cannot be used for uniformity assessment of powder components with the similar colours -Because of lighting conditions, the raw images need background correction
Electrical conductivity method	-Providing information on the whole volume of powder mixture -Easy to use -Low cost -Good for uniformity analysis of conductive materials	-Only applicable for blend uniformity assessment of a conductive material in the mixture of powders -Cannot be used for multicomponent mixing assessment
Tribo-electrification method	-Providing information on the whole powder mixtures -Easy to use	- Error due to off-line sampling and disturbance of the powder bed (invasive) -Unreliable tool because it

	-Economic	may be exposed to the variations in humidity, temperature and other environmental factors -Cannot be used for multicomponent mixing assessment
Thermal analytical method	-Easy to use and Low cost -Providing information on the whole powder mixture -Good for the determination of the end-point of mixing	-Error due to off-line sampling and disturbance of the powder bed (invasive) -Measurement must be performed quickly after sampling to reduce the heat exchange effect -This method should be checked on several powder systems with complex thermal event to judge whether it is suitable for powder uniformity assessment in general
X-ray microtomographic method	-Providing the three-dimensional structure of the objects non-invasively -Higher special resolution as compared to other tomographic techniques	-Expensive -Cannot be readily used for multicomponent mixing assessment -Safety issues due to X-rays -Material with similar structural properties cannot be

		differentiated easily
Positron emission particle tracking	-Produces a three-dimensional image of a process -Non-invasive uniformity evaluation of powders is achievable	-Expensive -This method mainly provides the tracking of a single particle as a representative of other particles -Cannot be used for multicomponent mixing assessment -Erroneous locations could be spotted using this technique due to scattering of gamma rays
Electrical capacitance tomography	-Providing the 3D cross-sectional view of a stream non-intrusively -Applicable in many harsh conditions such as high-pressure or high temperature	-Expensive -Hard to detect the exact component distribution due to low spatial resolution -This method is applicable just for powders with noticeable variation in permittivity or dielectric constant -Cannot be used for multicomponent mixing assessment
Magnetic resonance imaging tomography	-Providing information on 3D powder mixtures by constructing	-Expensive -Many particles get visible by

	cross-sectional images of raw data non-invasively	magnetic field via getting coated by detectable substances. This could change the surface properties of particles such as flowability -Cannot be readily for multicomponent mixing assessment
Near-infrared spectroscopy	-Fast chemical imaging technique -On-line/continuous monitoring of samples is possible using this technique -Applicable for multicomponent mixing assessment -Reasonable in price	-Overlapped spectra cause the minor component detection difficult -Light penetration to the sample is limited and therefore composition characterisation of the bulk of powders is hard to be achieved.
Raman spectroscopy	-Less overlapped spectra resulting in precise minor component detection (high spatial resolution) -Applicable for multicomponent mixing assessment	-Sometimes, interference by florescence may cause erroneous results -Expensive
Acoustic emission spectrometry	-Non-invasive/on-line particulate blend monitoring -Economic and easy to use -For on-line monitoring, no need of optically transparent window in the	-Representative for changes in powder composition at wall, rather than in the bulk of materials

	process	
Fluorescence spectroscopy	-Low cost and fast in data acquisition -Sensitivity of the method is higher than the absorption spectroscopy	-Sensitive to fluctuations in pH and temperature. -Applicability of the method depends on the strength of fluorescence of the studied component as compared to the fluorescence of other components within the mixture